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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

PAR PHARMACEUTICAL, INC and ALKERMES PHARMA IRELAND LIMITED Plaintiffs, v. BRECKENRIDGE PHARMACEUTICAL, INC., Defendant.	Case No. _____ CIVIL ACTION **COMPLAINT**

STATEMENT PURSUANT TO L. CIV. R. 10.1

Plaintiff Par Pharmaceutical, Inc. is a corporation organized under the laws of the State of Delaware and has a principal place of business at 300 Tice Boulevard, Woodcliff Lake, New

Jersey and Plaintiff Alkermes Pharma Ireland Limited is a corporation organized under the laws of Ireland having a principal place of business at Monksland, Athlone, Co. Westmeath, Ireland. Upon information and belief, Defendant Breckenridge Pharmaceutical, Inc. is a corporation organized under the laws of Florida having a principal place of business at 1141 S. Rogers Circle, Boca Raton, Florida and an office at 1 Passaic Avenue, Fairfield, New Jersey. For their Complaint against Defendant Breckenridge Pharmaceutical, Inc., Plaintiffs allege as follows:

NATURE OF THE ACTION

1. This is a civil action for infringement of United States Patent Nos. 6,592,903 (the "'903 patent") and 7,101,576 (the "'576 patent") pursuant to the Patent Laws of the United States, 35 U.S.C. § 1, *et seq.*

PARTIES

2. Plaintiff Par Pharmaceutical, Inc. ("Par") is a corporation organized under the laws of Delaware, with its principal place of business at 300 Tice Boulevard, Woodcliff Lake, New Jersey.

3. Plaintiff Alkermes Pharma Ireland Limited ("Alkermes") is an Irish corporation having a principal place of business at Monksland, Athlone, Co. Westmeath, Ireland.

4. Upon information and belief, Defendant is an entity organized under the laws of Florida, with its principal place of business at 1141 S. Rogers Circle, Boca Raton, Florida.

JURISDICTION

5. This Court has subject matter jurisdiction over this action under 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202, and 35 U.S.C. § 271(e)(2).

6. Upon information and belief, Defendant is in the business of making and selling generic pharmaceutical products, which it distributes, markets, and/or sells in New Jersey, and throughout the United States.

7. Upon information and belief, Defendant is registered to do business in New Jersey.

8. Upon information and belief, Defendant has a sales office in New Jersey located at 1 Passaic Avenue, Fairfield, NJ 07004.

9. Upon information and belief, Defendant has previously submitted to the jurisdiction of the United States District Court for the District of New Jersey, for example, in *Medpointe Healthcare Inc. v. Breckenridge Pharmaceutical, Inc.*, C.A. No. 03-656-HAA, *Bradley Pharmaceuticals, Inc. v. Breckenridge Pharmaceuticals, Inc.*, C.A. No. 06-2442-SDW-MCA; *Novartis Pharmaceuticals Corp. v. Breckenridge Pharmaceutical, Inc.*, C.A. No. 06-4199-FSH; *Everett Laboratories, Inc. V. Breckenridge Pharmaceutical, Inc.*, C.A. No. 08-3156-JLL-CCC; *Everett Laboratories, Inc. V. Breckenridge Pharmaceutical, Inc.*, C.A. No. 09-177-JLL-CCC.

10. This Court has personal jurisdiction over Defendant by virtue of, *inter alia*, Defendant's continuous and systematic contacts with corporate entities within this judicial district, its previous submission to the jurisdiction of this judicial district, its presence in this judicial district and its marketing and sales activities in this judicial district, including, but not limited to the substantial, continuous and systematic distribution, marketing and/or sales of generic pharmaceutical products to residents of this judicial district.

VENUE

11. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

PATENTS-IN-SUIT

12. Plaintiff Alkermes is the lawful owner of the ’903 patent.

13. The ’903 patent, entitled “Nanoparticulate Dispersions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate,” duly and legally issued on July 15, 2003, naming Niels P. Ryde and Stephen B. Ruddy as inventors. A copy of the ’903 patent is attached as Exhibit A.

14. Plaintiff Alkermes is the lawful owner of the ‘576 patent.

15. The ’576 patent, entitled “Nanoparticulate Megestrol Formulations,” duly and legally issued on September 5, 2006, naming Douglas Hovey, John Pruitt, and Tuula Ryde as inventors. A copy of the ’576 patent is attached as Exhibit B.

MEGACE® ES

16. Plaintiff Par is the holder of New Drug Application (“NDA”) No. 21-778 for Megace® ES (megestrol acetate) oral suspension, 125 mg/mL, and is an exclusive licensee of the ’576 and ’903 patents with respect to Megace® ES in the United States.

17. On July 5, 2005, the FDA approved NDA No. 21-778 for the manufacture, marketing, and sale of Megace® ES (megestrol acetate) oral suspension for the treatment of appetite loss, severe malnutrition, or unexplained, significant weight loss in AIDS patients. Plaintiff Par has sold Megace® ES under NDA No. 21-778 since its approval.

18. The ’903 and ’576 patents are listed in the FDA’s *Approved Drug Products with Therapeutic Equivalence Evaluations* (the “Orange Book”) as covering Par’s product Megace® ES.

DEFENDANT'S ANDA

19. Upon information and belief, Defendant submitted ANDA No. 20-4688 to the FDA under 35 U.S.C. § 355(j), seeking approval to engage in commercial manufacture, use, and/or sale of megestrol acetate oral suspension, 125 mg/mL, ("Defendant's Generic Product") before expiration of the '903 and '576 patents.

20. Upon information and belief, ANDA No. 20-4688 refers to and relies upon Plaintiff Par's NDA for Megace® ES and purports to contain data showing bioequivalence of Defendant's Generic Product with Megace® ES.

21. Plaintiffs received from Defendant a letter dated May 16, 2013 (the "Notification Letter"), stating that ANDA No. 20-4688 contains a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (a "Paragraph IV certification") alleging that the '903 and '576 patents are invalid, unenforceable, and/or will not be infringed by the manufacture, use, or sale of Defendant's Generic Product.

22. Plaintiffs commenced this action within 45 days of receiving the Notification Letter.

COUNT ONE

(Infringement of the '576 Patent under 35 U.S.C. § 271(e)(2))

23. Plaintiffs reallege paragraphs 1-22 above as if fully set forth herein.

24. Defendant's submission of ANDA No. 20-4688 to the FDA with a Paragraph IV certification regarding the '576 patent, seeking approval to engage in commercial manufacture, use, and/or sale of Defendant's Generic Product before the expiration of the '576 patent, constitutes infringement of the '576 patent under 35 U.S.C. § 271(e)(2)(A).

COUNT TWO

(Declaratory Judgment of Infringement of the '576 Patent under 35 U.S.C. § 271(a)-(c))

25. Plaintiffs reallege paragraphs 1-22 above as if fully set forth herein.

26. Upon information and belief, Defendant intends, soon after the FDA has approved its ANDA No. 20-4688, to begin the commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of Defendant's Generic Product.

27. Upon information and belief, Defendant has made, and will continue to make, substantial preparation in the United States to manufacture, use, offer to sell, or sell within the United States, and/or import into the United States, Defendant's Generic Product before expiration of the '576 patent.

28. Upon information and belief, Defendant has made, and will continue to make, substantial preparation in the United States to actively induce or contribute to the manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of Defendant's Generic Product before expiration of the '576 patent.

29. Defendant's actions, including without limitation the filing of ANDA No. 20-4688, exhibit a refusal to change the course of its action despite Plaintiffs' patent rights.

30. Upon information and belief, the commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of Defendant's Generic Product before expiration of the '576 patent, and the active inducement of and/or contribution to any of those activities, will constitute infringement, inducement of infringement and/or contributory infringement of the '576 patent.

31. Plaintiffs are entitled to a declaratory judgment that future commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of Defendant's Generic Product, or the inducement of and/or contribution to the

commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of Defendant's Generic Product before expiration of the '576 patent by Defendant or its agents, will constitute infringement, inducement of infringement and/or contributory infringement of the '576 patent.

COUNT THREE

(Infringement of the '903 Patent under 35 U.S.C. § 271(e)(2))

32. Plaintiffs reallege paragraphs 1-22 above as if fully set forth herein.

33. Defendant's submission of ANDA No. 20-4688 to the FDA with a Paragraph IV certification regarding the '903 patent, seeking approval to engage in commercial manufacture, use, and/or sale of Defendant's Generic Product before the expiration of the '903 patent, constitutes infringement of the '903 patent under 35 U.S.C. § 271(e)(2)(A).

COUNT FOUR

(Declaratory Judgment of Infringement of the '903 Patent under 35 U.S.C. § 271(a)-(c))

34. Plaintiffs reallege paragraphs 1-22 above as if fully set forth herein.

35. Upon information and belief, Defendant intends, soon after the FDA has approved its ANDA No. 20-4688, to begin the commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of Defendant's Generic Product.

36. Upon information and belief, Defendant has made, and will continue to make, substantial preparation in the United States to manufacture, use, offer to sell, or sell within the United States, and/or import into the United States, Defendant's Generic Product before expiration of the '903 patent.

37. Upon information and belief, Defendant has made, and will continue to make, substantial preparation in the United States to actively induce or contribute to the manufacture,

use, offer to sell, or sale within the United States, and/or importation into the United States, of Defendant's Generic Product before expiration of the '903 patent.

38. Defendant's actions, including without limitation the filing of ANDA No. 20-4688, exhibit a refusal to change the course of its action despite Plaintiffs' patent rights.

39. Upon information and belief, the commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of Defendant's Generic Product before expiration of the '903 patent, and the active inducement of and/or contribution to any of those activities, will constitute infringement, inducement of infringement and/or contributory infringement of the '903 patent.

40. Plaintiffs are entitled to a declaratory judgment that future commercial manufacture, use, offer to sell, or sale within the United States, and/or importation into the United States, of Defendant's Generic Product, or the inducement of and/or contribution to the commercial manufacture, use, offer for sale, or sale within the United States, and/or importation into the United States, of Defendant's Generic Product before expiration of the '903 patent by Defendant or its agents, will constitute infringement, inducement of infringement and/or contributory infringement of the '903 patent.

INJUNCTIVE RELIEF

41. Plaintiffs will be substantially and irreparably damaged and harmed by Defendant's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

EXCEPTIONAL CASE

42. Defendant has at all relevant times been aware of the ’576 and ’903 patents, and has had no good faith basis for its infringement of that patent. This is an exceptional case under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that this Court:

A. Enter a judgment that Defendant has infringed the ’576 patent under 35 U.S.C. § 271(e)(2)(A) by submitting ANDA No. 20-4688 to the FDA, seeking approval to engage in commercial manufacture, use, offer to sell or sale of Defendant’s Generic Product before expiration of the ’576 patent;

B. Enter a declaration under 28 U.S.C. § 2201 that Defendant would infringe the ’576 patent under one or more of 35 U.S.C. §§ 271(a)-(c) by its manufacture, use, offer to sell or sale within the United States, or importation into the United States, of Defendant’s Generic Product before expiration of the ’576 patent;

C. Enter a judgment that Defendant has infringed the ’903 patent under 35 U.S.C. § 271(e)(2)(A) by submitting ANDA No. 20-4688 to the FDA, seeking approval to engage in commercial manufacture, use, offer to sell or sale of Defendant’s Generic Product before expiration of the ’903 patent;

D. Enter a declaration under 28 U.S.C. § 2201 that Defendant would infringe the ’903 patent under one or more of 35 U.S.C. §§ 271(a)-(c) by its manufacture, use, offer to sell or sale within the United States, or importation into the United States, of Defendant’s Generic Product before expiration of the ’903 patent;

E. Enter an order under 35 U.S.C. § 271(e)(4)(A) that the earliest effective approval date of ANDA No. 20-4688, if any, shall be no earlier than the date of expiration of each patent-in-suit Defendant is found to infringe, including any extensions;

F. Enter an injunction under 35 U.S.C. §§ 271(e)(4)(b) and 283 permanently enjoining Defendant, its officers, agents, servants, employees, licensees, representatives, and attorneys, and all other persons acting or attempting to act in concert or participation with them or on their behalf, from engaging in commercial manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of Defendant's Generic Product before the expiration of each patent-in-suit Defendant is found to infringe, including any extensions;

G. Grant Plaintiffs compensatory damages in an amount to be determined at trial including both pre-judgment and post-judgment interest if Defendant commercially manufactures, uses, offers to sell, or sells in the United States, or imports into the United States, Defendant's Generic Product before the expiration of each patent-in-suit Defendant is found to infringe, including any extensions;

H. Declare that Defendant's activities have made this an exceptional case under 35 U.S.C. § 285 and grant Plaintiffs their attorneys' fees; and

I. Award Plaintiffs any further and additional relief as this Court may deem just and proper.

Dated: June 27, 2013

LATHAM & WATKINS LLP

By s/ Gina R. Gencarelli
Gina R. Gencarelli

Attorneys for Plaintiff Par Pharmaceutical, Inc.

THE LAW OFFICE OF
JASON B. LATTIMORE, ESQ., LLC

By s/ Jason B. Lattimore
Jason B. Lattimore

Attorneys for Plaintiff Alkermes Pharma Ireland Limited

CERTIFICATION PURSUANT TO L. CIV. R. 11.2

I hereby certify that the matter in controversy is also the subject of *Par Pharmaceutical, Inc. & Alkermes Pharma Ireland Limited v. Breckenridge Pharmaceuticals, Inc.*, Civil Action No. 1:13-cv-01114, currently pending in the United States District Court for the District of Delaware. I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

By: s/ Gina R. Gencarelli
Gina R. Gencarelli

By: s/ Jason B. Lattimore
Jason B. Lattimore

Dated: June 27, 2013

EXHIBIT A

US006592903B2

(12) **United States Patent**
Ryde et al.

(10) **Patent No.: US 6,592,903 B2**
(45) **Date of Patent: *Jul. 15, 2003**

(54) **NANOPARTICULATE DISPERSIONS COMPRISING A SYNERGISTIC COMBINATION OF A POLYMERIC SURFACE STABILIZER AND DIOCTYL SODIUM SULFOSUCCINATE**

(75) Inventors: **Niels P. Ryde**, Malvern, PA (US); **Stephen B. Ruddy**, Schwenksville, PA (US)

(73) Assignee: **Elan Pharma International Ltd.**, Shannon (IE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 61 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/075,443**

(22) Filed: **Feb. 15, 2002**

(65) **Prior Publication Data**

US 2002/0110597 A1 Aug. 15, 2002

Related U.S. Application Data

(63) Continuation of application No. 09/666,539, filed on Sep. 21, 2000.

(51) **Int. Cl.**[7] **A61K 9/00**; A61K 9/14

(52) **U.S. Cl.** **424/489**; 424/509; 424/45; 424/466; 424/434

(58) **Field of Search** 424/489, 509, 424/45, 466, 434

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(List continued on next page.)

FOREIGN PATENT DOCUMENTS

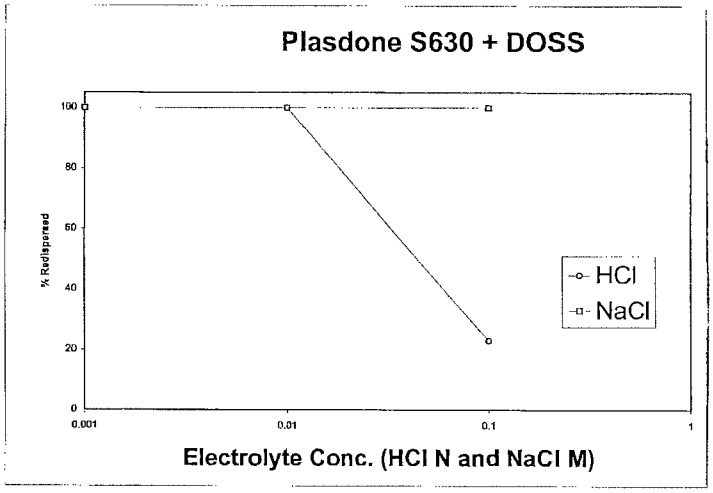
WO	96/25918	8/1996
WO	98/35666	8/1998
WO	00/18374	4/2000
WO	00/27363	5/2000

Primary Examiner—Michael G. Hartley
Assistant Examiner—M. Haghighatian
(74) *Attorney, Agent, or Firm*—Foley & Lardner

(57) **ABSTRACT**

Disclosed are solid dose nanoparticulate compositions comprising a poorly soluble active agent, at least one polymeric surface stabilizer, and dioctyl sodium sulfosuccinate (DOSS). The solid dose compositions exhibit superior redispersibility of the nanoparticulate composition upon administration to a mammal, such as a human or animal. The invention also describes methods of making and using such compositions.

33 Claims, 1 Drawing Sheet



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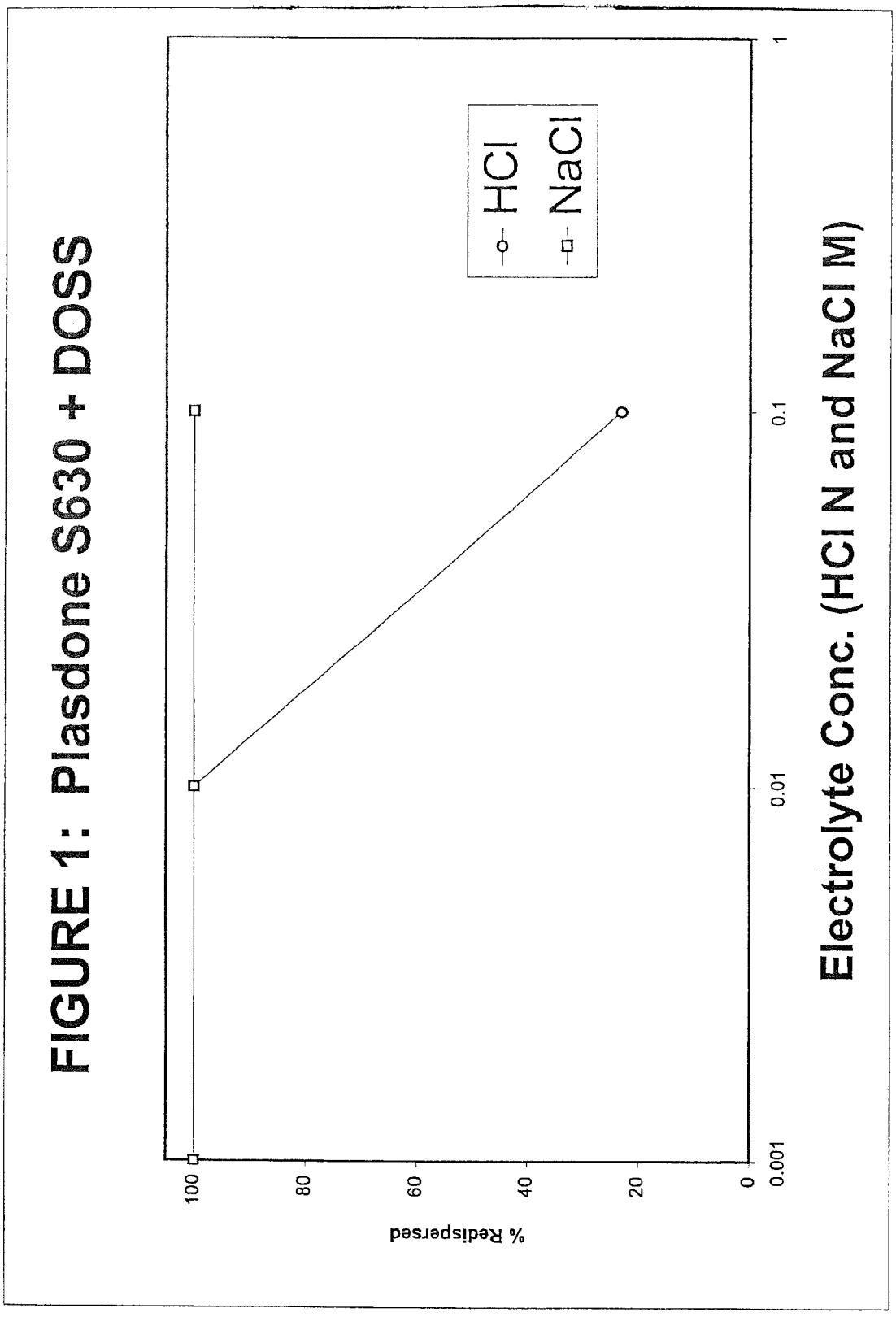


FIGURE 1: Plasdone S630 + DOSS
HCl
NaCl
% Redispersed
100
80
60
40
20
0
0.001
0.01
0.1
1
Electrolyte Conc. (HCl N and NaCl M)

NANOPARTICULATE DISPERSIONS COMPRISING A SYNERGISTIC COMBINATION OF A POLYMERIC SURFACE STABILIZER AND DIOCTYL SODIUM SULFOSUCCINATE

This application is a continuation of Ser. No. 09/666,539 filed Sep. 21, 2000.

FIELD OF THE INVENTION

The present invention is directed to solid dose nanoparticulate compositions having a synergistic combination of at least one polymeric surface stabilizer and dioctyl sodium sulfosuccinate (DOSS). The solid dose compositions exhibit superior redispersion of the nanoparticulate composition either upon administration to a mammal, such as a human or animal, or reconstitution in an aqueous electrolyte solution.

BACKGROUND OF THE INVENTION

A. Background Regarding Nanoparticulate Compositions

Nanoparticulate compositions, first described in U.S. Pat. No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto the surface thereof a non-crosslinked surface stabilizer. This invention is an improvement over that disclosed in the '684 patent, as the '684 patent does not describe the use of synergistic combinations of polymeric surface stabilizers and DOSS in solid dose compositions.

Prior U.S. patents teach the use of DOSS as a primary or secondary surface stabilizer for nanoparticulate compositions. See e.g., U.S. Pat. No. 5,145,684, for "Surface Modified Drug Nanoparticles;" U.S. Pat. No. 5,302,401, for "Method to Reduce Particle Size Growth During Lyophilization;" U.S. Pat. No. 5,318,767, for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,336,507, for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,346,702, for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" U.S. Pat. No. 5,399,363, for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,401,492, for "Water-Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824, for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" U.S. Pat. No. 5,451,393, for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440, for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583, for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,494,683, for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,503,723, for "Isolation of Ultra Small Particles;" U.S. Pat. No. 5,510,118, for "Process for Preparing Therapeutic Compositions Containing Nanoparticles;" U.S. Pat. No. 5,543,133, for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,552,160, for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931, for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,560,932, for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Pat. No. 5,571,536, for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,580,579, for "Site-Specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" U.S. Pat. No. 5,587,143, for "Butylene Oxide-Ethylene Oxide Block Copolymer Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" U.S. Pat. No. 5,593,657, for "Novel Barium Salt Formulations Stabilized by Non-Ionic and Anionic Stabilizers;" U.S. Pat. No. 5,628,981, for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,665,331, for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Pat. No. 5,716,642, for "Microprecipitation of Nanoparticulate Pharmaceutical Agents Using Surface Active Material Derived from Similar Pharmaceutical Agents;" U.S. Pat. No. 5,718,919, for "Nanoparticles Containing the R(−) Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001, for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025, for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829, for "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" and U.S. Pat. No. 6,068,858, for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers." In addition, several published international applications teach the usefulness of DOSS as a primary or secondary surface stabilizer for nanoparticulate compositions. See e.g., WO 98/35666, for "Formulations of Nanoparticle Naproxen Tablets;" WO 00/18374, for "Controlled Release Nanoparticulate Compositions;" WO 96/25918, for "Aerosols Containing Nanoparticulate Dispersions;" and WO 00/27363, for "Aerosols Comprising Nanoparticle Drugs."

Prior art patents also teach the use of DOSS as a cloud point modifier for nanoparticulate surface stabilizers. See e.g., U.S. Pat. No. 5,298,262, for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,326,552, for "Novel Formulation for Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weigh Non-ionic Surfactants;" U.S. Pat. No. 5,346,702, for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" U.S. Pat. No. 5,352,459, for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,447,710, for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-Ionic Surfactants;" U.S. Pat. No. 5,565,188, for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,665,330, for "Dual Purpose Diagnostic/Therapeutic Agent Having a Tri-Iodinated Benzoyl Group Linked to a Coumarin."

And several prior art references teach the use of DOSS in nanoparticulate compositions as both a surface stabilizer and as a cloud point modifier for a primary surface stabilizer. See e.g., U.S. Pat. No. 5,466,433, for "Polyiodinated Aroyloxy Esters;" U.S. Pat. No. 5,472,683, for "Nanoparticle Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204, for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,521,218, for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No. 5,525,328, for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic Systems Imaging;" U.S. Pat. No. 5,534,270, for "Method of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,573,

749, for "Nanoparticulate Diagnostic Mixed Carboxylic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750, for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,603,916, for "3,5-Bis-[Alkanoyl Amino]-2,4,6-Triiodobenzyl Esters;" U.S. Pat. No. 5,643,552, for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,668,196, for "3-Amido-Triiodophenyl Esters as X-Ray Contrast Agents;" and U.S. Pat. No. 5,670,136, for "2,4,6-Triiodo-5-Substituted-Amino-Isophthalate Esters Useful as X-Ray Contrast Agents for Medical Diagnostic Imaging."

U.S. Pat. No. 5,585,108, for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays," claims a nanoparticulate dispersion including, inter alia, a water-insoluble particulate drug, a surfactant which can be a polymeric stabilizer, such as hydroxypropyl methylcellulose, a pharmaceutically acceptable clay, and a secondary stabilizer, such as DOSS or sodium lauryl sulfate. See col. 7 of the patent. This reference differs from the present invention in that it is directed to a nanoparticulate dispersion, and not a solid dose nanoparticulate formulation.

U.S. Pat. No. 5,298,262, for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization," describes the use of DOSS in a nanoparticulate composition as an anionic surfactant useful in raising the cloud point of a surface stabilizer. According to the '262 patent, by raising the cloud point of the surface stabilizer of a nanoparticulate composition, the composition can be heat sterilized without producing particle aggregation because of the exposure to elevated temperatures. Liquid compositions are heat sterilized, not powders. This is because sterile products are not manufactured for oral administration because of the cost, complexity, etc. Thus, this patent does not teach or suggest the use of DOSS in a solid dose formulation to increase redispersion of the nanoparticulate composition upon administration to a mammal, such as a human or animal, or reconstitution in an aqueous electrolyte solution.

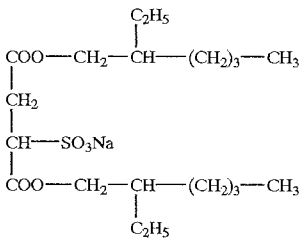
Finally, U.S. Pat. No. 5,518,738, for "Nanoparticulate NSAID Compositions," describes a nanoparticulate solid dose of an NSAID having a film of polyvinylpyrrolidone (PVP), hygroscopic sugar, and sodium lauryl sulfate adsorbed on the surface of the drug. In the examples of this patent, solid films of the nanoparticulate composition with various redispersants are prepared, including DOSS. In contrast to the present invention, the '738 patent teaches that a solid film of a nanoparticulate drug, DOSS, and PVP shows'extremely poor redispersibility. Thus, this reference teaches away from the present invention.

Many of the prior art patents listed above also teach the usefulness of polymeric surface stabilizers for nanoparticulate compositions, such as hydroxypropyl cellulose, hydroxypropyl methyl cellulose, and polyvinylpyrrolidone.

However, the prior art does not teach or suggest the use of synergistic combinations of polymeric surface stabilizers and DOSS in solid dose compositions of nanoparticulate active agents. Nor does the prior art teach or suggest that such synergistic compositions can result in superior redispersion of the nanoparticulate composition upon administration to a mammal, such as a human or animal, or reconstitution in an aqueous electrolyte solution.

B. Background Regarding DOSS

DOSS is an anionic surfactant commercially available from a variety of sources, including Chemax Inc. (Greenville, S.C.), Finetex Inc. (Elmwood Park, N.J.), R. W. Greeff & Co. (Greenwich, Conn.), McIntyre Group Ltd. (Chicago, Ill.), Penta Mfg. Co. (Livingston, N.J.), Rhone-Poulenc Inc. Specialty Chemicals Div., (Cranbury, N.J.), RTD Chemicals Corp. (Hackettown, N.J.), Scher Chemicals Inc. (Clifton, N.J.), Spectrum Quality Products Inc. (Gardena, Calif.), Thornley Co. Inc. (Wilmington, Del.), and Van Waters & Rogers (Kirkland, Wash.). It has the chemical formula $C_{20}H_{37}O_7S.Na$ and the following structure:



DOSS is a widely used wetting agent and dispersant. It is a white, waxlike, plastic solid added to powdered gelatins, drink mixes, and cocoas to make them dissolve more quickly and completely in liquids. It is also used as a stabilizer in pharmaceuticals, chewing gums, and canned milks, and is added to shampoos, bath products, and skin cleansers. While the U.S. Food and Drug Administration (FDA) limits the amount of DOSS that can be used in food and drug products, it still rates the compound generally recognized as safe (GRAS). 21 C.F.R. §172.810.

There is a need in the art for solid dose nanoparticulate compositions exhibiting superior redispersion of the nanoparticulate composition upon administration to a mammal, such as a human or animal, or reconstitution in an aqueous electrolyte solution. The present invention satisfies this need.

SUMMARY OF THE INVENTION

The present invention is directed to the surprising and unexpected discovery that solid dose nanoparticulate compositions comprising at least one polymeric surface stabilizer and DOSS exhibit superior redispersion of the nanoparticulate composition upon administration to a mammal, such as a human or animal, or reconstitution in an aqueous electrolyte solution. The solid dose nanoparticulate compositions comprise at least one poorly soluble active agent, at least one polymeric surface stabilizer adsorbed to the surface of the active agent, and DOSS.

Another aspect of the invention is directed to pharmaceutical compositions comprising a solid dose nanoparticulate composition of the invention. The pharmaceutical composition comprises at least one poorly soluble active agent, at least one polymeric surface stabilizer adsorbed to the surface of the drug, DOSS, and a pharmaceutically acceptable carrier, as well as any desired excipients.

This invention further discloses methods of making a nanoparticulate composition having at least one polymeric surface stabilizer adsorbed on the surface of the active agent and DOSS. Such a method comprises contacting a poorly soluble nanoparticulate active agent with at least one polymeric surface stabilizer and DOSS under time and conditions sufficient to provide a nanoparticle active agent/surface stabilizer/DOSS composition. Some or all of the polymeric surface stabilizers and DOSS can be contacted with the active agent either before, during, or after size reduction of the active agent.

The present invention is further directed to methods of treatment comprising administering to a mammal in need a therapeutically effective amount of a nanoparticulate composition according to the invention.

Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1: Shows the % redispersion in an electrolyte solution, as a function of the concentration of the electrolyte solution, for a spray dried nanoparticulate MAP kinase inhibitor composition.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to the surprising and unexpected discovery that solid dose nanoparticulate compositions having at least one polymeric surface stabilizer and DOSS exhibit dramatically superior redispersion of the nanoparticulate composition upon administration to a mammal, such as a human or animal, or upon reconstitution of a dry powder prepared from a nanoparticulate composition in an aqueous electrolyte solution. The electrolyte concentration should be representative of physiological conditions found in the human body. Representative electrolyte solutions can be, but are not limited to, 0.1, 0.01, or 0.001 N HCL, and/or 0.1, 0.01, or 0.001 M NaCl, and combinations thereof. Of these electrolyte solutions, 0.01 N HCl, 0.1 M NaCl, and combinations thereof are most representative of human physiological conditions.

Prior to the present invention, liquid dispersions and solid dose forms of nanoparticulate compositions were known. One frequent problem of prior art solid dose nanoparticulate compositions was that upon administration to a mammal, such as a human or animal, the nanoparticulate composition would not redisperse, and thus the solid dose composition would lose the benefits afforded by formulating the composition into a nanoparticulate form. This is because nanoparticulate compositions benefit from the small particle size of the active agent; if the active agent does not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated drug particles are formed. With the formation of such agglomerated particles, the bioavailability of the composition drops dramatically below that observed with the liquid dispersion form of the drug.

Most drugs are marketed in a solid dose form, such as a tablet, capsule, etc. This is because such dosage forms are easy to store and transport. In addition, such dosage forms are easily marketed. Patient compliance is high, as compared with injectable forms of drugs. Thus, it is critical to develop solid dose forms of nanoparticulate compositions which exhibit the same benefits observed with the liquid dispersion form of the compositions.

It was discovered that solid dose nanoparticulate compositions having at least one polymeric surface stabilizer and DOSS exhibit dramatic redispersion of the nanoparticulate composition upon administration to a mammal, such as a human or animal, or reconstitution in an aqueous electrolyte solution. DOSS or polymeric stabilizers alone cannot produce highly redispersible solid dose nanoparticulate compositions. In combination, however, the two compounds exhibit a synergistic effect of stabilizing the active agent and resulting in dramatic redispersion of the solid dose nanoparticulate composition upon administration to a mammal, such as a human or animal, or reconstitution in an aqueous electrolyte solution.

Another benefit of the invention is that DOSS is highly tolerated by the human body, in contrast to other dispersants such as SLS, for which the human body has a low tolerance. DOSS can be given to humans in large doses on a chronic basis, as the FDA has approved the use of DOSS as a stool softener at doses of up to 500 mg/daily for adults, and in children over 6 months old up to 75 mg/day. *See Handbook of Pharmaceutical Excipients,* Third Edition, p. 189 (American Pharmaceutical Association, 2000). The dosage of DOSS employed in the present invention is below the threshold amount which produces laxative effects.

The combination of DOSS and a polymeric surface stabilizer was tested on a wide variety of drugs, including Mitogen-Activated protein (MAP) kinase inhibitor, an analgesic, and an angiogenesis inhibitor. Thus, the phenomenon of high redispersibility is not limited to a specific drug or drug class. However, the phenomenon is limited to nanoparticulate compositions comprising at least one polymeric surface stabilizer and DOSS. Other types of surface stabilizers formulated with DOSS, such as ampiphilic stabilizers having hydrophobic and hydrophilic ends, have not been found to produce solid dose compositions having comparable redispersion properties.

A. Nanoparticulate Compositions

The nanoparticulate compositions of the invention comprise a nanoparticulate active agent, such as a drug, having at least one polymeric surface stabilizer adsorbed on the surface thereof and DOSS. The nanoparticulate active agent compositions, comprising a nanoparticulate active agent and at least one polymeric surfactant, have an effective average particle size prior to incorporation in a solid dose form of less than about 1 micron, less than about 800 nm, less than about 600 nm, less than about 400 nm, and less than about 200 nm.

Upon administration to a mammal, such as a human or animal, or reconstitution in an electrolyte solution, the solid dose nanoparticulate composition redisperses such that 960% of the active agent particles have a particle size of less than about (1) 5 microns, when the nanoparticulate dispersion, prior to incorporation into a solid dose form, has an effective average particle size of less than about 1 micron; (2) 4 microns, when the nanoparticulate dispersion, prior to incorporation into a solid dose form, has an effective average particle size of less than about 800 nm; (3) 3 microns, when the nanoparticulate dispersion, prior to incorporation into a solid dose form, has an effective average particle size of less than about 600 nm; (4) 2 microns, when the nanoparticulate dispersion, prior to incorporation into a solid dose form, has an effective average particle size of less than about 400 nm; and (5) 1 micron, when the nanoparticulate dispersion, prior to incorporation into a solid dose form, has an effective average particle size of less than about 200 nm.

1. Drug Particles

The nanoparticles of the invention comprise a therapeutic or diagnostic agent, collectively referred to as a "drug," which is poorly soluble in at least one medium. By "poorly soluble" it is meant that the drug has a solubility in the liquid dispersion medium of less than about 10 mg/mL, and preferably of less than about 1 mg/mL. A therapeutic agent can be a pharmaceutical agent, including biologics such as proteins, peptides, and nucleotides, or a diagnostic agent, such as a contrast agent, including x-ray contrast agents. The drug is preferably present in an essentially pure form, is

dispersible in at least one liquid medium, and exists either as a discrete, crystalline phase, or as an amorphous phase. The crystalline phase differs from a non-crystalline or amorphous phase which results from precipitation techniques, such as those described in EP Patent No. 275,796.

The drug can be selected from a variety of known classes of drugs, including, for example, proteins, peptides, nucleotides, anti-obesity drugs, nutriceuticals, corticosteroids, elastase inhibitors, analgesics, anti-fungal, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, anti-muscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives (hypnotics and neuroleptics), astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (antiparkinsonian agents), haemostatics, immuriological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radiopharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators and xanthines.

The drugs are commercially available and/or can be prepared by techniques known in the art.

2. Surface Stabilizers

Polymeric surface stabilizers useful herein physically adhere to the surface of the nanoparticulate active agent, but do not chemically react with the drug or itself. Individually adsorbed molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

The polymeric surface stabilizer is adsorbed on the surface of the active agent in an amount sufficient to maintain an effective average particle size of less than about 1 micron. Two or more surface stabilizers can be employed in the compositions and methods of the invention.

Representative examples of suitable polymeric surface stabilizers include, but are not limited to polyvinylpyrrolidone (PVP), cellulose ethers such as, but not limited to, hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, methyl cellulose, and hydroxyethyl cellulose, polysaccharides such as, but not limited to, dextrin, guar gum, starch, random copolymers of vinyl acetate and vinyl pyrrolidone, such as Plasdone® S630 (ISP), Kollidone® VA 64 (BASF), polyvinyl alcohol, copolymers of vinylacetate and vinylalcohol.

Plasdone® S630 is a random copolymer of vinyl pyrrolidone and vinyl acetate, in a 60:40 ratio. Other random copolymers of vinyl pyrrolidone and vinyl acetate can also be used in the invention having, for example, ratios of vinyl pyrrolidone to vinyl acetate of 90:10, 80:20, or 50:50. Preferably, the random copolymer contains at least 50% vinyl pyrrolidone.

The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

3. Nanoparticulate Drug/Surface Stabilizer Particle Size

As used herein, particle size is determined on the basis of the weight average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, dynamic and static light scattering, and disk centrifugation.

By "an effective average particle size of less than about 1 micron" it is meant that at least 90% of the active agent particles have a particle size of less than about 1 micron when measured by the above techniques. In other embodiments, the nanoparticulate active agent compositions, comprising a nanoparticulate active agent and at least one polymeric surfactant, have an effective average particle size prior to incorporation in a solid dose form of less than about 800 nm, less than about 600 nm, less than about 400 nm, and less than about 200 nm.

Upon administration to a mammal, such as a human or animal, or reconstitution in an electrolyte solution, the solid dose nanoparticulate composition redisperses such that 90% of the active agent particles have a particle size of less than about (1) 5 microns, when the nanoparticulate dispersion, prior to incorporation into a solid dose form, has an effective average particle size of less than about 1 micron; (2) 4 microns, when the nanoparticulate dispersion, prior to incorporation into a solid dose form, has an effective average particle size of less than about 800 nm; (3) 3 microns, when the nanoparticulate dispersion, prior to incorporation into a solid dose form, has an effective average particle size of less than about 600 nm; (4) 2 microns, when the nanoparticulate dispersion, prior to incorporation into a solid dose form, has an effective average particle size of less than about 400 nm; and (5) 1 micron, when the nanocrystal dispersion, prior to incorporation into a solid dose form, has an effective average particle size of less than about 200 nm.

4. Other Pharmaceutical Excipients

Pharmaceutical compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (SMCC).

Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and accsulfame K. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

Suitable disintegrants include corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, crosspovidone, sodium starch glycolate, and mixtures thereof.

Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the acid component of the effervescent couple may be present.

5. Concentration of Nanoparticulate Drug, Surface Stabilizers and DOSS

The relative amount of drug, one or more polymeric surface stabilizers, and DOSS can vary widely. The optimal amount of the polymeric surface stabilizers can depend, for example, upon the particular drug selected, the equivalent hydrophilic lipophilic balance (HLB) of the drug, the melting point, cloud point, and water solubility of the polymeric surface stabilizer, and the surface tension of water solutions of the stabilizer, etc.

The concentration of the one or more polymeric surface stabilizers can vary from about 0.01 to about 90%, from about 1 to about 75%, from about 10 to about 60%, or from about 10 to about 55% by weight based on the total combined dry weight of the drug substance and surface stabilizer, not including other excipients.

The concentration of the drug can vary from about 99.8% to about 0.1%, from about 80% to about 5.0%, or from about 50% to about 10% by weight based on the total combined dry weight of the drug and polymeric surface stabilizer, not including other excipients.

The concentration of DOSS can vary from about 0.1 to about 20%, and from about 1 to about 10%, based on the total dry weight of the drug, surface stabilizer, and DOSS, not including other excipients.

B. Methods of Making Nanoparticulate Formulations

The nanoparticulate drug compositions can be made using, for example, milling or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in the '684 patent.

1. Milling to Obtain Nanoparticulate Drug Dispersions

Milling of aqueous drug dispersions to obtain a nanoparticulate dispersion comprises dispersing poorly soluble drug particles in a liquid dispersion medium, followed by applying mechanical means in the presence of grinding media to reduce the particle size of the drug to the desired effective average particle size. The drug particles can be reduced in size in the presence of at least one polymeric surface stabilizer and/or DOSS. Alternatively, the drug particles may be contacted with one or more polymeric surface stabilizers and/or DOSS after attrition. Other compounds, such as a diluent, can be added to the drug/surface stabilizer composition during the size reduction process. Dispersions can be manufactured continuously or in a batch mode. The resultant nanoparticulate drug dispersion can be utilized in solid dosage formulations, such as controlled release dosage formulations, solid dose fast melt formulations, aerosol formulations, tablets, capsules, etc.

2. Precipitation to Obtain Nanoparticulate Drug Compositions

Another method of forming the desired nanoparticulate composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble drugs in the presence of one or more polymeric surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving the poorly water-soluble drug in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one polymeric surface stabilizer and DOSS to form a solution; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means. The resultant nanoparticulate drug dispersion can be dried and used in a solid dose composition.

3. Methods of Drying Nanoparticulate Dispersions

The nanoparticulate liquid dispersion formed by either milling or precipitation can be dried prior to formulating the composition into a solid dose form for administration.

Powders comprising nanoparticulate drug can be made by spray-drying aqueous dispersions of a nanoparticulate drug, polymeric surface stabilizer, and DOSS to form a dry powder which consists of aggregated drug/polymeric surface stabilizer/DOSS nanoparticles. Alternatively, the aqueous dispersion of drug, polymeric surface stabilizer, and DOSS can contain a dissolved diluent, such as lactose or mannitol, which when spray dried forms diluent particles, each of which contains at least one embedded drug nanoparticle combined with a polymeric surface stabilizer and DOSS.

Nanoparticulate drug dispersions can also be freeze-dried to obtain powders suitable for formulation into solid dose forms. Such powders comprise aggregated nanoparticulate drug particles having a polymeric surface stabilizer and DOSS. Freeze dried powders can also be obtained by freeze drying aqueous dispersions of drug, polymeric surface stabilizer, and DOSS, which additionally contain a dissolved diluent such as lactose or mannitol. In these instances the freeze dried powders consist of particles of diluent, each of which contains at least one embedded drug nanoparticle combined with a polymeric surface stabilizer and DOSS.

Other known methods of processing liquid dispersions, and which can be employed in the present invention, include granulation, including but not limited to high shear granulation, fluid bed granulation, roto granulation, and melt granulation. Additional methods such as spray coating and extrusion spherization can also be used. Any other conventional method for drying or otherwise processing a liquid dispersion can also be used in the invention.

C. Methods of Using Nanoparticulate Drug Formulations Comprising One or More Polymeric Surface Stabilizers and DOSS

The solid dose nanoparticulate compositions of the present invention can be administered to humans and animals in any pharmaceutically acceptable manner, such as orally, rectally, pulmonary, intravaginally, locally (powders, ointments or drops), or as a buccal or nasal spray. Solid dosage forms for oral administration include capsules, tablets, pills, powders, pellets, and granules. In such solid dosage forms, the nanoparticulate drug is admixed with at least one of the following: (a) one or more inert excipients (or carrier), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar—agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol

monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Actual dosage levels of the drug in the nanoparticulate compositions of the invention may be varied to obtain an amount of active ingredient that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the drug, the desired duration of treatment, and other factors.

The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

EXAMPLE 1

The purpose of this example was to compare the redispersion properties of various solid dose nanoparticulate ketoprofen compositions in which DOSS is added to a nanoparticulate dispersion following milling and spray drying (rather than during the milling process). Ketoprofen. also known as m-benzoylhydratopic acid, is a nonsteroidal anti-inflammatory analgesic.

A ketoprofen nanoparticulate dispersion was prepared, having 15% ketoprofen, 1.5% PVP K29/32, and 0.075% SLS. The dispersion was prepared using a Dyno®-Mill (Type: KDL; Mfg.: Willy A Bachofen AG, Basel, Switzerland) equipped with a 150 cc batch chamber using a 500 μm milling media of type Polymill500® for 2 hrs at 10° C.

The ketoprofen nanoparticulate dispersion (ketoprofen NCD) was then spray dried with various excipients, as shown in Table 1, using a Büchi Mini Spray Dryer B-191 (B üchi Switzerland). Following spray drying, the redispersion properties of each spray dried ketoprofen powder were tested by measuring the ketoprofen particle size following redispersion and dilution with saturated ketoprofen solution, without sonication and following 1 minute sonication. Particle size was measured using a Horiba LA910 particle sizer. The results of the redispersion tests are also shown in Table 1, below.

TABLE 1

Redispersion Comparison of Nanoparticulate Ketoprofen Spray Dried Powder

Com-tion	Formula	Redispersed Particle Size (nm) (No sonication/1 min. sonication) Mean	D90*	% under 1000 nm
A	no additives	3801/3725	7697/7152	12.8/12.8
B	Drug:mannitol 1:1.2	6836/4050	15415/11173	41.8/52.2
C	Drug:Mannitol:DOSS 1:1.2:0.08	1860/1055	8785/453	84.6/90.1
D	Drug:Maltrin150** 1:1.2	20665/6104	38879/14479	9.2/26.6
E	Drug:Mannitol:DOSS 1:0.6:0.08	17149/2737	72756/10229	55.4/75.0
F	Drug:Xylitol 1:1	11241/5277	43502/12536	65.0/67.8

TABLE 1-continued

Redispersion Comparison of Nanoparticulate Ketoprofen Spray Dried Powder

Com-tion	Formula	Redispersed Particle Size (nm) (No sonication/1 min. sonication) Mean	D90*	% under 1000 nm
G	Drug:Xylitol:DOSS 1:1:0.08	1936/501	390/269	90.2/95.6
H	Drug:Mannitol:DOSS 1:1:0.08	4069/1944	15113/8313	72.6/80.0
I	Drug:Xylitol:DOSS 1:1:0.02	11469/2168	42333/7702	64.1/75.2
J	Drug:Mannitol:DOSS 1:1:0.08	2963/2004	10800/8011	72.2/77.5
K	Drug:Xylitol:DOSS 1:0.75:0.08	654/332	273/251	95.0/98.2

*90% of the particles are below this size.
**maltodextrin

The results dramatically show the effect DOSS has on the redispersibility of the spray dried nanoparticulate ketoprofen composition. Following redispersion, less than 13% of the ketoprofen particles of Composition A, lacking any additives (i.e., just spray dried ketoprofen NCD), had a particle size of less than a micron. Similarly, following redispersion less than 52.2% (following sonication) of the ketoprofen particles of Composition B, containing only mannitol as an additive, had a particle size of less than a micron. In contrast, following redispersion 90.1% (following sonication) of the ketoprofen particles of Composition C, containing mannitol and DOSS as additives, had a particle size of less than a micron. Thus, DOSS resulted in a 75% increase in the amount of particles having a particle size of under 1 micron following redispersion. This is significant as smaller drug particles result in greater bioavailability of the drug.

The amount of DOSS in relation to other excipients also affects the redispersion properties of the solid dose nanoparticulate drug composition. Thus, by varying the amount of DOSS and other excipients, redispersion of a solid dose nanoparticulate composition can be optimized. For example, Composition C, having a Drug:Mannitol:DOSS ratio of 1:1.2:0.08 showed 90.1% of the ketoprofen particles (following sonication) having a particle size of less than 1 micron following redispersion. However, Composition E, having a Drug:Mannitol:DOSS ratio of 1:0.6:0.08, showed 75.0% of the ketoprofen particles (following sonication) having a particle size of less than 1 micron following redispersion; Compositions H and J, having a Drug:Mannitol:DOSS ratios of 1:1:0.08, showed 80.0% and 77.5%, respectively, of the ketoprofen particles (following sonication) having a particle size of less than 1 micron following redispersion.

Similar results were obtained with spray dry excipients other than mannitol. For example, Composition F, having a Drug:Xylitol ratio of 1:1, showed 67.8% of the ketoprofen particles (following sonication) having a particle size of less than 1 micron following redispersion. In contrast, Compositions G and K, having Drug:Xylitol:DOSS ratios of 1:1:0.08 and 1:0.75:0.08, respectively, showed 95.6% and 98.2%, respectively, of the ketoprofen particles (following sonication) having a particle size of less than 1 micron following redispersion. This is an increase of 41% (Composition G) and 45% over the results obtained with Composition F, lacking DOSS.

This example demonstrates the effectiveness of adding DOSS to form a highly redispersible solid dose nanoparticulate composition, when DOSS is added following mill-

ing but before spray drying of the nanoparticulate dispersion. Other examples demonstrate the addition of DOSS to the nanoparticulate dispersion during milling. Thus, the time of addition of DOSS during preparation of the pharmaceutical composition is not critical to the goal of obtaining a highly redispersible composition.

EXAMPLE 2

The purpose of this example was to evaluate the redispersion properties of a solid dose nanoparticulate ketoprofen composition comprising DOSS and a polymeric stabilizer in an electrolyte solution. This example differs from Example 1 in that DOSS is added directly to the nanoparticulate dispersion (NCD) during milling, followed by preparation of a solid dose composition.

A ketoprofen nanoparticulate dispersion was prepared, having the composition 5% ketoprofen, 1.% PVP K29/32, and 0.2% DOSS. The dispersion was prepared using a Dyno®-Mill (Type: KDL; Mfg.: Willy A Bachofen A G, Basel Switzerland) equipped with a 150 cc batch chamber using a 500 μm milling media of type Polymill500® for 2 hrs at 10° C.

The ketoprofen nanoparticulate dispersion (ketoprofen NCD) was then spray dried with mannitol, with a drug to mannitol ratio of 1:1 using a Büchi Mini Spray Dryer B-191 (Büchi Switzerland). The redispersion properties of the spray dried ketoprofen in water are shown below in Table 2.

TABLE 2

	Redispersion Properties of Ketoprofen Spray Dried NCD Containing DOSS in Water					
Time (days)	Mean (no sonication)	Mean (1 min. sonication)	D_{50} (1 min. sonication)	D_{50} (no sonication)	D_{90} (1 min. sonication)	D_{90} (no sonication)
0	118	121	105	107	192	198
1	152	163	144	155	219	233

All measurements are in nanometers (nm).

The results of the redispersion test show excellent redispersion of the spray dried nanoparticulate ketoprofen composition comprising DOSS.

The redispersion properties of the same spray dried ketoprofen composition were then tested in electrolyte solutions, which mimic the conditions found in the human gastrointestinal tract. The results of these tests are shown in Table 3, below.

TABLE 3

		Redispersion Properties of Ketoprofen Spray Dried NCD Comprising DOSS in an Electrolyte Solution					
Electrolyte Conc. (M)	Type	no sonic. Mean	No. sonic. Small %	No. sonic. Large %	1 min. sonic. Mean	1 min. sonic. Small %	No. sonic. Large %
0	—	172	100	0	182	100	0
0.001	HCl	535	97	3	166	100	0
0.01	HCl	176	100	0	188	100	0
0.1	HCl	17756	2	98	5908	8	92
0.001	NaCl	178	100	0	191	100	0
0.01	NaCl	151	100	0	163	100	0
0.1	NaCl	186	100	0	204	100	0

All particle sizes are in nanometers (nm).

"Small" particles are defined as those below 1 micron (1000 nm) and "large" particles are those above 1 micron. Electrolyte concentrations of 0.001 HCl, 0.01 HCl, and 0.1 HCl correspond to pH 3, pH 2, and pH 1, respectively. In the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Thus, a 0.01 N HCl concentration simulates typical acidic conditions found in the stomach. 0.1 M NaCl simulates the electrolyte concentration found throughout the body, including the intestine.

The results show that under acidic to neutral pH conditions, the nanoparticulate ketoprofen solid dose composition showed excellent redispersion properties, with 100% of the nanoparticulate particles having a redispersed particle size of less than 1 micron. In addition, under all but the most acidic conditions of 0.1 M HCl (which are not typically representative of human gastric pH), the nanoparticulate ketoprofen solid dose composition showed excellent redispersion properties, with almost 100% of the nanoparticulate particles having a redispersed particle size of less than 1 micron.

EXAMPLE 3

The purpose of this example was to evaluate the redispersion properties of a solid dose nanoparticulate MAP kinase inhibitor composition comprising DOSS and a polymeric stabilizer in electrolyte solutions.

5% (w/w) of Compound A, a MAP kinase inhibitor, 1% Plasdone® S630, and 0.2% DOSS were milled using a Dyno®-Mill (Type: KDL; Mfg.: Willy A Bachofen A G, Basel Switzerland) equipped with a 150 cc batch chamber using a 500 μm milling media of type Polymill500® for 3 hrs at 10° C.

The nanoparticulate MAP kinase inhibitor dispersion (NCD) was then spray dried at a drug to mannitol ratio of 1:1

using a Büchi Mini Spray Dryer B-191 (Büchi Switzerland). The redispersion properties of the spray dried MAP kinase inhibitor in electrolyte solutions are shown below in Table 4 and in FIG. 1. A Horiba LA910 particle sizer was used to measure particle size. "Small" particles were defined as those below 1 micron and "large" particles were defined as those above 1 micron.

TABLE 4

Redispersion Properties of a MAP Kinase Inhibitor Spray Dried NCD Comprising DOSS and a Polymeric Stabilizer in an Electrolyte Solution

Electrolyte Conc. (M)	Type	no sonic. Mean	No. sonic. Small %	No.sonic. Large %	1 min. sonic. Mean	1 min. sonic. Small %	No. sonic. Large %
0	---	99	100	0	99	100	0
0.001	HCl	100	100	0	100	100	0
0.01	HCl	105	100	0	106	100	0
0.1	HCl	4708	23	77	1901	52	48
0.001	NaCl	103	100	0	103	100	0
0.01	NaCl	101	100	0	101	100	0
0.1	NaCl	105	100	0	105	100	0

All particle sizes are in nanometers (nm).

The results show that the solid dose nanoparticulate MAP kinase inhibitor composition, comprising DOSS and a polymeric stabilizer, showed excellent redispersion in all tested electrolyte media representative of in vivo conditions. Even at a higher acid concentration of 0.1 N HCl, the composition showed over 50% of the drug particles of the composition having a small particle size following 1 minute of sonication.

EXAMPLE 4

The purpose of this example was to evaluate the redispersion properties of a solid dose nanoparticulate angiogenesis inhibitor composition comprising DOSS and a polymeric stabilizer, which has been spray granulated with various excipients, in water and in electrolyte solutions.

Nanocrystalline dispersions (NCD) of an angiogenesis inhibitor, Compound C, were made by milling the ingredients shown for each composition in Table 7. Samples A and B were milled on a Netzch Mill (Netzsch Inc., Exton, Pa.), having a LMZ 2L chamber, for 11 hrs. 500 micron PolyMill media was used. Processing temperatures ranged from 11.6° C. to 27.4° C. Samples C–E were milled on a Dyno® Mill, having a 150 cc chamber, at a temperature of 10° C. for 3 hours, also using 500 micron PolyMill media.

Following milling, the additives listed in Table 5 were added to the nanoparticulate dispersion until dissolved, followed by spraying of the dispersion over a fluidized mannitol excipient, also provided in Table 5, to form a solid dose composition. A Glatt GPCG-1 fluid bed processor (Glatt Air Technologies, Inc., Ramsey, N.J.) was used for this process.

TABLE 5

Spray Granulated Nanoparticulate Angiogenesis Inhibitor Compositions

Sample	Formula	Particle Size of Nanocrystal Dispersion (nm)	Additives	Fluidized Mannitol
A	15% Drug + 3.75% PVP K29/32 and 0.15% SLS	mean 105 nm; D_{90} of 167 nm	Drug mannitol ratio of 1:0.75	Pearlitol ® SD200
B	15% Drug + 3.75% PVP K29/32 and 0.15% SLS	mean 105 nm; D_{90} of 167 nm	Drug mannitol ratio of 1:0.75	Pearlitol ® SD200
C	15% Drug + 3.75% PVP K29/32, 0.15% SLS, and 0.1% sodium ascorbate	mean of 101 nm; D_{90} of 165 nm	Drug mannitol ratio of 1:0.75	Mannitol 35
D	15% Drug + 3.75% PVP K29/32, 0.15% SLS, and 0.1% sodium ascorbate	mean of 101 nm; D_{90} of 165 nm	Drug:mannitol ratio of 1:0.75	Mannitol 35
E	15% Drug + 3.75% PVP K29/32, 0.15% SLS, and 0.1% sodium ascorbate	mean of 101 nm; D_{90} of 165 nm	Drug:mannitol ratio of 1:0.75 and stabilizer DOSS ratio of 1:0.2	Mannitol 35

Each composition A–E, comprising drug/excipient granules, was then milled to a uniform particle size in a Quadro Comill (Model 193; also called a cone mill, which comprises fixed stationary screens and a rotating impeller), to produce Compositions A2–E2. The milling process comprised passing the powder through the mill (one pass through, about 2–5 minutes).

The redispersibility, in water and various electrolyte solutions, was then measured for the solid dose nanoparticulate angiogenesis compositions, both Compositions A–E (unmilled) and A2–E2 (milled), as shown in Table 6.

TABLE 6

Redispersibility of Spray Granulated Nanoparticulate Angiogenesis Inhibitor Compositions (Milled and Unmilled Granulate Compositions)

		No Sonication			1 Min. Sonication		
Composition	Redisp. Media	Mean (nm)	D90 (nm)	% Under 1000 nm	Mean (nm)	D90 (nm)	% Under 1000 nm
A	water	5265	11776	26.2	1440	4717	70.8
(unmilled)	0.01 N HCl	12160	27244	9.4	3034	6997	36.1
	0.01 M NaCl	7487	15324	11.6	2274	6504	57.6
A2	water	5777	12463	23.0	2538	7547	62.9
(milled)	0.01 N HCl	58519	236602	5.3	3573	7929	30
	0.01 M NaCl	8341	17698	11	1975	5366	54.9
B	water	8222	18365	18.5	4368	9033	51.5
(unmilled)	0.01 N HCl	83643	264545	4.8	4238	9458	26.3
	0.01 M NaCl	14863	33139	8	2579	6561	45.8
B2	water	18897	55523	14.2	2691	7294	50
(milled)	0.01 N HCl	44037	103747	4.1	5161	11771	22.4
	0.01 M NaCl	13514	29820	6.8	2547	6163	42.1
C	water	3124	8088	46.9	422	645	93.4
(unmilled)	0.01 N HGl	6713	14117	16.6	2471	6285	47
	0.01 M NaCl	4103	9426	30.6	904	3006	80.4
C2	water	3150	8427	49	1071	3602	83.6
(milled)	0.01 N HCl	8728	19180	17.1	3039	7626	43.3
	0.01 M NaCl	4544	9896	25.5	1278	4345	75
D	water	3094	7865	44.8	342	569	97.3
(unmilled)	0.01 N HCl	9630	21697	14.8	2762	7043	45.3
	0.01 M NaCl	4295	8561	20.6	1475	5034	73.6
D2	water	2162	5885	54.4	295	488	98.7
(milled)	0.01 N HCl	8885	20181	16.9	1982	5087	51.7
	0.01 M NaCl	4410	8710	19	1066	3420	75.9
E	water	2186	7520	69.9	384	614	98.3
(unmilled)	0.01 N HCl	2161	7812	73.4	297	492	99
	0.01 M NaCl	2544	8755	68.1	357	588	98.5
E	water	2711	9141	66.6	436	672	93.6
(milled)	0.01 N HCl	2014	7608	75.9	291	483	99.1
	0.01 M NaCl	2203	8075	74.1	292	484	99

Only Sample E comprises DOSS. The redispersibility results showed that only this sample showed substantially improved redispersion in electrolyte media, with a redispersibility of 99.1% in 0.01 N HCl and 99% in 0.01 M NaCl. In contrast, Samples A–D showed redispersibility in 0.01 N HCl of from 22.4% (Sample B2) to 51.7% (Sample D2), and a redispersibility in 0.01 N HCl of from to 42.1% (Sample B2) to 80.4% (Sample C). The results are dramatic as the only difference between Sample E and Samples C and D was the presence (Sample E) or absence (Samples C and D) of DOSS.

The results demonstrate the dramatically superior redispersibility properties of a solid dose nanoparticulate formulation comprising DOSS.

It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

We claim:

1. A nanoparticulate dispersion comprising:
(a) a poorly soluble active agent;
(b) at least one polymeric surface stabilizer adsorbed on the surface of the active agent; and
(c) about 0.1% to about 20% w/w of dioctyl sodium sulfosuccinate (DOSS),
wherein the effective average particle size of the poorly soluble active agent in the nanoparticulate dispersion is less than about 1 micron.

2. The dispersion of claim 1, wherein the active agent is present in an amount of about 99.8% to about 0.1% (w/w).

3. The dispersion of claim 1, wherein the active agent is present in an amount of about 80% to about 5% (w/w).

4. The dispersion of claim 1, wherein the active agent is present in an amount of about 50% to about 10% (w/w).

5. The dispersion of claim 1, wherein the at least one polymeric surface stabilizer is present in an amount of about 0.01% to about 90% (w/w).

6. The dispersion of claim 1, wherein the at least one polymeric surface stabilizer is present in an amount of about 1% to about 75% (w/w).

7. The dispersion of claim 1, wherein the at least one polymeric surface stabilizer is present in an amount of about 10% to about 60% (w/w).

8. The dispersion of claim 1, wherein DOSS is present in an amount of about 1% to about 10% (w/w).

9. The dispersion of claim 1, wherein the effective average particle size of the nanoparticulate dispersion is less than about 800 nm.

10. The dispersion of claim 1, wherein the effective average particle size of the nanoparticulate dispersion is less than about 600 nm.

11. The dispersion of claim 1, wherein the effective average particle size of the nanoparticulate dispersion is less than about 400 nm.

12. The dispersion of claim 1, wherein the effective average particle size of the nanoparticulate dispersion is less than about 200 nm.

13. The dispersion of claim 1, wherein the active agent is selected from the group consisting of a crystalline phase, a semi-crystalline phase, and an amorphous phase.

14. The dispersion of claim 1, wherein the active agent is selected from the group consisting of proteins, peptides, nucleotides, anti-obesity drugs, nutraceuticals, corticosteroids, elastase inhibitors, analgesics, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants, diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics, haemostatics, immuriological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones, anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

15. The dispersion of claim 1, wherein the active agent is ketoprofen.

16. The dispersion of claim 1, wherein the active agent is a MAP kinase inhibitor.

17. The dispersion of claim 1, wherein the active agent is an angiogenesis inhibitor.

18. The dispersion of claim 1, wherein the at least one polymeric surface stabilizer is selected from the group consisting of polyvinylpyrrolidone, cellulose ethers, polysaccharides, random copolymers of vinyl acetate and vinyl pyrrolidone, polyvinyl alcohol, and copolymers of vinyl acetate and vinyl alcohol.

19. The dispersion of claim 18, wherein the at least one polymeric surface stabilizer is selected from the group consisting of hydroxypropyl cellulose, hydroxypropyl methylcellulose, carboxymethyl cellulose, methyl cellulose, hydroxyethyl cellulose, dextrin, guar gum, starch, and a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in a mass proportion of 3:2.

20. A pharmaceutical composition comprising the dispersion of claim 1, and one or more pharmaceutically acceptable excipients.

21. A method of making a nanoparticulate dispersion comprising:

(a) dispersing particles of a poorly soluble active agent in a liquid dispersion medium; and

(b) applying mechanical means in the presence of grinding media to reduce the effective average particle size of the active agent in the liquid dispersion medium to less than about 1 micron, wherein at least one polymeric surface stabilizer and dioctyl sodium sulfosuccinate are added to the liquid dispersion medium before or after milling.

22. The method of claim 21, wherein the active agent is present in an amount of about 99.8 to about 0.1% (w/w).

23. The method of claim 21, wherein the at least one polymeric surface stabilizer is present in an amount of about 0.01% to about 90% (w/w).

24. The method of claim 21, wherein DOSS is added in an amount of about 0.1% to about 20% (w/w).

25. The method of claim 21, wherein DOSS is added in an amount of about 1.0% to about 10% (w/w).

26. The method of claim 21, wherein the active agent is selected from the group consisting of a crystalline phase drug, a semi-crystalline phase drug, and an amorphous phase drug.

27. The method of claim 21, wherein the effective average particle size of the resultant nanoparticulate dispersion is less than about 800 nm.

28. The method of claim 21, wherein the effective average particle size of the resultant nanoparticulate dispersion is less than about 600 nm.

29. The method of claim 21, wherein the effective average particle size of the resultant nanoparticulate dispersion is less than about 400 nm.

30. The method of claim 21, wherein the effective average particle size of the nanoparticulate dispersion is less than about 200 nm.

31. The dispersion of claim 1, wherein the active agent is selected from the group consisting of ketoprofen, a MAP kinase inhibitor, and an angiogenesis inhibitor.

32. The pharmaceutical composition of claim 20, wherein the active agent is selected from the group consisting of ketoprofen, a MAP kinase inhibitor, and an angiogenesis inhibitor.

33. The method of claim 21, wherein the active agent is selected from the group consisting of ketoprofen, a MAP kinase inhibitor, and an angiogenesis inhibitor.

* * * * *

EXHIBIT B

US007101576B2

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Hovey et al.

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(54) **NANOPARTICULATE MEGESTROL FORMULATIONS**

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(52) **U.S. Cl.** **424/490**; 424/489; 424/491; 424/493; 424/494; 424/496; 424/497; 424/498; 514/169

(58) **Field of Classification Search** 424/489, 424/400, 451, 464; 514/169
See application file for complete search history.

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(57) **ABSTRACT**

The present invention is directed to nanoparticulate compositions comprising megestrol. The megestrol particles of the composition have an effective average particle size of less than about 2000 nm.

31 Claims, 3 Drawing Sheets

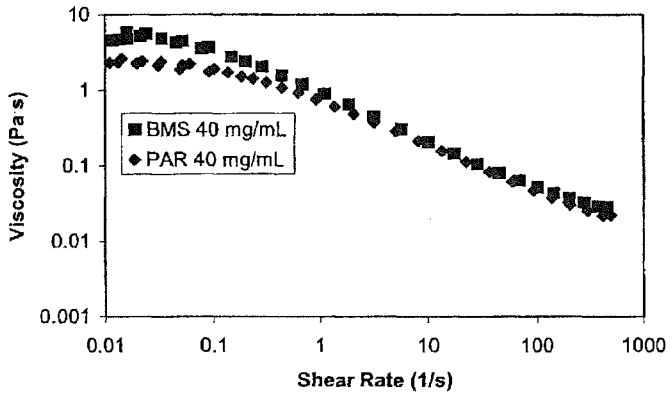

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FIGURE 1

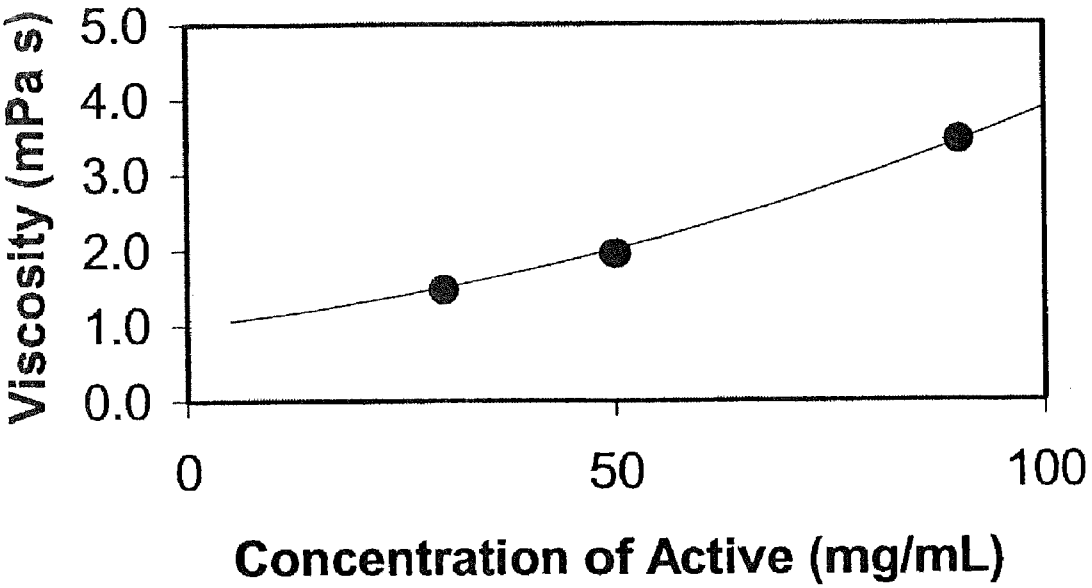

Viscosity (mPa s)
5.0
4.0
3.0
2.0
1.0
0.0
0
50
100
Concentration of Active (mg/mL)

FIGURE 2

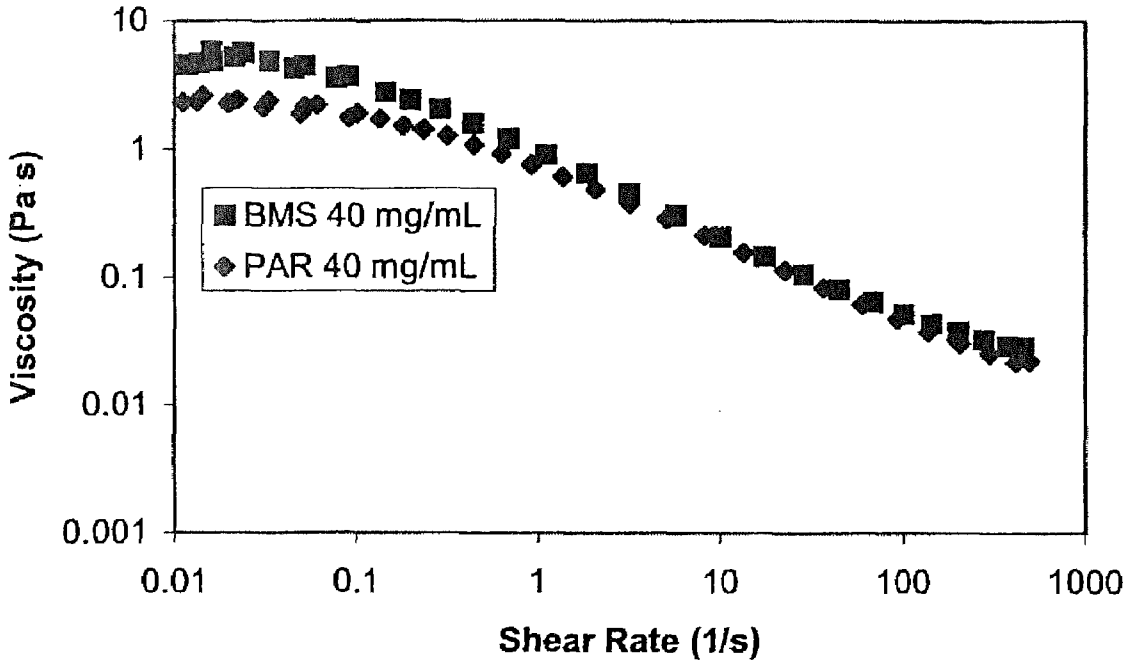
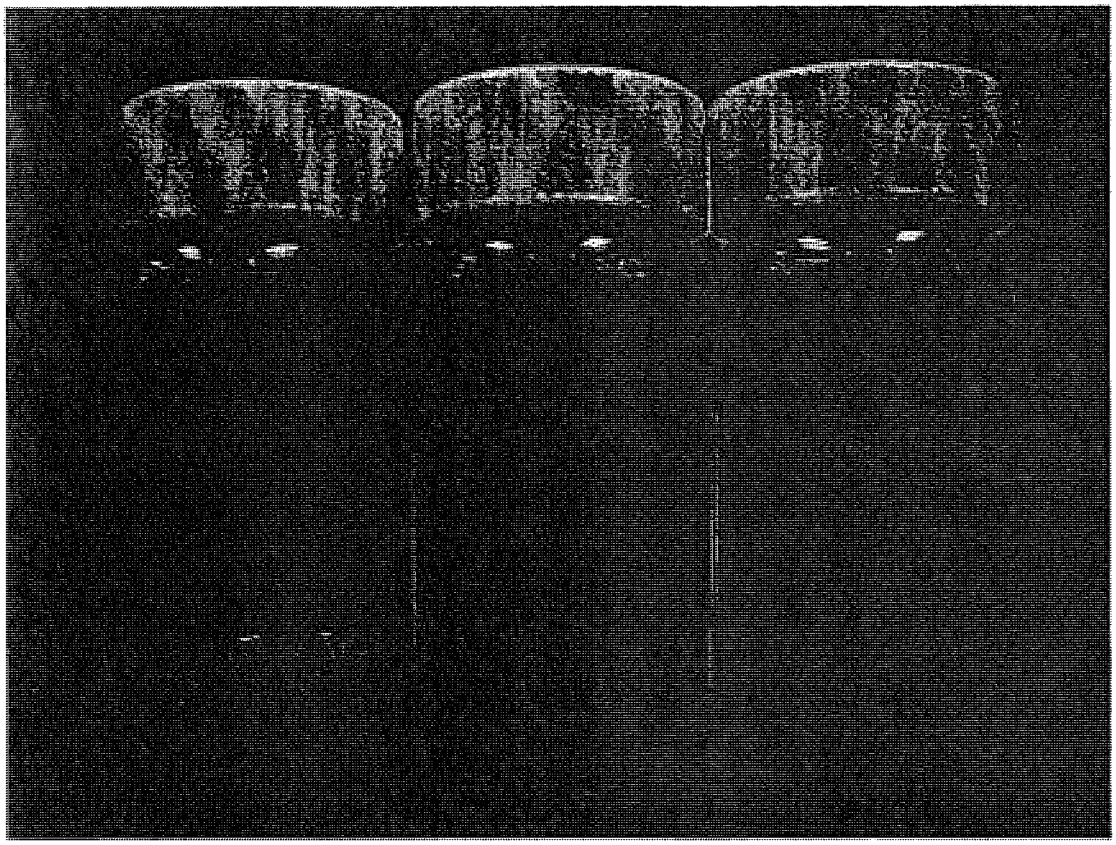

10
1
0.1
0.01
0.001
Viscosity (Pa s)
BMS 40 mg/mL
PAR 40 mg/mL
0.01
0.1
1
10
100
1000
Shear Rate (1/s)

FIGURE 3



NANOPARTICULATE MEGESTROL FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to a nanoparticulate composition comprising megestrol and preferably at least one surface stabilizer associated with the surface of the drug. The nanoparticulate megestrol particles have an effective average particle size of less than about 2000 nm.

BACKGROUND OF THE INVENTION

A. Background Regarding Nanoparticulate Compositions

Nanoparticulate compositions, first described in U.S. Pat. No. 5,145,684 ("the '684 patent"), are particles consisting of a poorly soluble therapeutic or diagnostic agent having adsorbed onto the surface thereof a non-crosslinked surface stabilizer. The '684 patent does not describe nanoparticulate compositions of megestrol.

Methods of making nanoparticulate compositions are described, for example, in U.S. Pat. Nos. 5,518,187 and 5,862,999, both for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388, for "Continuous Method of Grinding Pharmaceutical Substances;" and U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Nanoparticulate compositions are also described, for example, in U.S. Pat. No. 5,298,262 for "Use of Ionic Cloud Point Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,302,401 for "Method to Reduce Particle Size Growth During Lyophilization;" U.S. Pat. No. 5,318,767 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,326,552 for "Novel Formulation For Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,328,404 for "Method of X-Ray Imaging Using Iodinated Aromatic Propanedioates;" U.S. Pat. No. 5,336,507 for "Use of Charged Phospholipids to Reduce Nanoparticle Aggregation;" U.S. Pat. No. 5,340,564 for "Formulations Comprising Olin 10-G to Prevent Particle Aggregation and Increase Stability;" U.S. Pat. No. 5,346,702 for "Use of Non-Ionic Cloud Point Modifiers to Minimize Nanoparticulate Aggregation During Sterilization;" U.S. Pat. No. 5,349,957 for "Preparation and Magnetic Properties of Very Small Magnetic-Dextran Particles;" U.S. Pat. No. 5,352,459 for "Use of Purified Surface Modifiers to Prevent Particle Aggregation During Sterilization;" U.S. Pat. No. 5,399,363 and U.S. Pat. No. 5,494,683, both for "Surface Modified Anticancer Nanoparticles;" U.S. Pat. No. 5,401,492 for "Water Insoluble Non-Magnetic Manganese Particles as Magnetic Resonance Enhancement Agents;" U.S. Pat. No. 5,429,824 for "Use of Tyloxapol as a Nanoparticulate Stabilizer;" U.S. Pat. No. 5,447,710 for "Method for Making Nanoparticulate X-Ray Blood Pool Contrast Agents Using High Molecular Weight Non-ionic Surfactants;" U.S. Pat. No. 5,451,393 for "X-Ray Contrast Compositions Useful in Medical Imaging;" U.S. Pat. No. 5,466,440 for "Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation;" U.S. Pat. No. 5,472,683 for "Nanoparticulate Diagnostic Mixed Carbamic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,500,204 for "Nanoparticulate Diagnostic Dimers as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,518,738 for "Nanoparticulate NSAID Formulations;" U.S. Pat. No. 5,521,218 for "Nanoparticulate Iododipamide Derivatives for Use as X-Ray Contrast Agents;" U.S. Pat. No. 5,525,328 for "Nanoparticulate Diagnostic Diatrizoxy Ester X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,552,160 for "Surface Modified NSAID Nanoparticles;" U.S. Pat. No. 5,560,931 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,565,188 for "Polyalkylene Block Copolymers as Surface Modifiers for Nanoparticles;" U.S. Pat. No. 5,569,448 for "Sulfated Non-ionic Block Copolymer Surfactant as Stabilizer Coatings for Nanoparticle Compositions;" U.S. Pat. No. 5,571,536 for "Formulations of Compounds as Nanoparticulate Dispersions in Digestible Oils or Fatty Acids;" U.S. Pat. No. 5,573,749 for "Nanoparticulate Diagnostic Mixed Carboxylic Anydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,573,750 for "Diagnostic Imaging X-Ray Contrast Agents;" U.S. Pat. No. 5,573,783 for "Redispersible Nanoparticulate Film Matrices With Protective Overcoats;" U.S. Pat. No. 5,580,579 for "Site-specific Adhesion Within the GI Tract Using Nanoparticles Stabilized by High Molecular Weight, Linear Poly(ethylene Oxide) Polymers;" U.S. Pat. No. 5,585,108 for "Formulations of Oral Gastrointestinal Therapeutic Agents in Combination with Pharmaceutically Acceptable Clays;" U.S. Pat. No. 5,587,143 for "Butylene Oxide-Ethylene Oxide Block Copolymers Surfactants as Stabilizer Coatings for Nanoparticulate Compositions;" U.S. Pat. No. 5,591,456 for "Milled Naproxen with Hydroxypropyl Cellulose as Dispersion Stabilizer;" U.S. Pat. No. 5,593,657 for "Novel Barium Salt Formulations Stabilized by Non-ionic and Anionic Stabilizers;" U.S. Pat. No. 5,622,938 for "Sugar Based Surfactant for Nanocrystals;" U.S. Pat. No. 5,628,981 for "Improved Formulations of Oral Gastrointestinal Diagnostic X-Ray Contrast Agents and Oral Gastrointestinal Therapeutic Agents;" U.S. Pat. No. 5,643,552 for "Nanoparticulate Diagnostic Mixed Carbonic Anhydrides as X-Ray Contrast Agents for Blood Pool and Lymphatic System Imaging;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,919 for "Nanoparticles Containing the R(−)Enantiomer of Ibuprofen;" U.S. Pat. No. 5,747,001 for "Aerosols Containing Beclomethasone Nanoparticle Dispersions;" U.S. Pat. No. 5,834,025 for "Reduction of Intravenously Administered Nanoparticulate Formulation Induced Adverse Physiological Reactions;" U.S. Pat. No. 6,045,829 "Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,068,858 for "Methods of Making Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors Using Cellulosic Surface Stabilizers;" U.S. Pat. No. 6,153,225 for "Injectable Formulations of Nanoparticulate Naproxen;" U.S. Pat. No. 6,165,506 for "New Solid Dose Form of Nanoparticulate Naproxen;" U.S. Pat. No. 6,221,400 for "Methods of Treating Mammals Using Nanocrystalline Formulations of Human Immunodeficiency Virus (HIV) Protease Inhibitors;" U.S. Pat. No. 6,264,922 for "Nebulized Aerosols Containing Nanoparticle Dispersions;" U.S. Pat. No. 6,267,989 for "Methods for Preventing Crystal Growth and Particle Aggregation in Nanoparticle Compositions;" U.S. Pat. No. 6,270,806 for "Use of PEG-Deriva-

tized Lipids as Surface Stabilizers for Nanoparticulate Compositions;" U.S. Pat. No. 6,316,029 for "Rapidly Disintegrating Solid Oral Dosage Form," U.S. Pat. No. 6,375,986 for "Solid Dose Nanoparticulate Compositions Comprising a Synergistic Combination of a Polymeric Surface Stabilizer and Dioctyl Sodium Sulfosuccinate," U.S. Pat. No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers;" U.S. Pat. No. 6,431,478 for "Small Scale Mill;" and U.S. Pat. No. 6,432,381 for "Methods for Targeting Drug Delivery to the Upper and/or Lower Gastrointestinal Tract," all of which are specifically incorporated by reference. In addition, U.S. patent application No. 20020012675 A1, published on Jan. 31, 2002, for "Controlled Release Nanoparticulate Compositions," describes nanoparticulate compositions, and is specifically incorporated by reference.

Amorphous small particle compositions are described, for example, in U.S. Pat. No. 4,783,484 for "Particulate Composition and Use Thereof as Antimicrobial Agent;" U.S. Pat. No. 4,826,689 for "Method for Making Uniformly Sized Particles from Water-Insoluble Organic Compounds;" U.S. Pat. No. 4,997,454 for "Method for Making Uniformly-Sized Particles From Insoluble Compounds;" U.S. Pat. No. 5,741,522 for "Ultrasmall, Non-aggregated Porous Particles of Uniform Size for Entrapping Gas Bubbles Within and Methods;" and U.S. Pat. No. 5,776,496, for "Ultrasmall Porous Particles for Enhancing Ultrasound Back Scatter."

B. Background Regarding Megestrol

Megestrol acetate, also known as 17α-acetyloxy-6-methylpregna-4,6-diene-3,20-dione, is a synthetic progestin with progestational effects similar to those of progesterone. It is used in abortion, endometriosis, and menstrual disorders. It is also used in a variety of situations including treatment of breast cancer, contraception, and hormone replacement therapy in post-menopausal women. Megestrol acetate is also frequently prescribed as an appetite enhancer for patients in a wasting state, such as HIV wasting, cancer wasting, or anorexia. In combination with ethynyl estradiol it acts as an oral contraceptive. It is also administered to subjects after castration.

Megestrol acetate is marketed by Par Pharmaceuticals, Inc. and under the brand name Megace® by Bristol Myers Squibb Co. Typical commercial formulations are relatively large volume. For example, Par Pharmaceuticals, Inc. megestrol acetate oral suspension contains 40 mg of micronized megestrol acetate per ml, and the package insert recommends an initial adult dosage of megestrol acetate oral suspension of 800 mg/day (20 mL/day). The commercial formulations of megestrol acetate are highly viscous suspensions, which have a relatively long residence time in the mouth and any tubing. Highly viscous substances are not well accepted by patient populations, particularly patients suffering wasting and those that are intubated.

U.S. Pat. No. 6,028,065 for "Flocculated Suspension of Megestrol Acetate," assigned to Pharmaceutical Resources, Inc. (Spring Valley, N.Y.), describes oral pharmaceutical micronized megestrol acetate compositions in the form of a stable flocculated suspension in water. The compositions comprise at least one compound selected from the group consisting of polyethylene glycol, propylene glycol, glycerol, and sorbitol; and a surfactant, wherein polysorbate and polyethylene glycol are not simultaneously present. U.S. Pat. No. 6,268,356, also for "Flocculated Suspension of Megestrol Acetate," and assigned to Pharmaceutical Resources, Inc., describes methods of treating a neoplastic condition comprising administering the composition of U.S. Pat. No. 6,028,065.

Another company that has developed a megestrol formulation is Eurand (Milan, Italy). Eurand's formulation is a modified form of megestrol acetate having increased bioavailability. Eurand structurally modifies poorly soluble drugs to increase their bioavailability. See www.eurand-.com. For megestrol acetate, Eurand uses its' "Biorise" process, in which a New Physical Entity (NPE) is created by physically breaking down megestrol's crystal lattice. This results in drug nanocrystals and/or amorphous drug, which are then stabilized with biologically inert carriers. Eurand uses three types of carriers: swellable microparticles, composite swellable microparticles, and cyclodextrins. See e.g., http://www.eurand.com/page.php?id=39. Such a delivery system can be undesirable, as "breaking down" an active agent's crystalline structure can modify the activity of the active agent. A drug delivery system which does not alter the structure of the active agent is preferable.

Among the progestins, megestrol acetate is one of the few that can be administered orally because of its reduced first-pass (hepatic) metabolism, compared to the parent hormone. In addition, it is claimed to be superior to 19-nor compounds as an antifertility agent because it has less effect on the endometrium and vagina. See *Stedman 's Medical Dictionary,* 25th Ed., page 935 (Williams & Wilkins, MD 1990). There is a need in the art for megestrol formulations which exhibit increased bioavailability, less variability, and/or less viscosity as compared to conventional microparticulate megestrol formulations. The present invention satisfies these needs.

SUMMARY OF THE INVENTION

The invention relates to nanoparticulate megestrol compositions. The compositions comprise megestrol and preferably at least one surface stabilizer associated with the surface of the megestrol particles. The nanoparticulate megestrol particles have an effective average particle size of less than about 2000 nm.

Another aspect of the invention is directed to pharmaceutical compositions comprising a nanoparticulate megestrol composition of the invention. The pharmaceutical compositions preferably comprise megestrol, at least one surface stabilizer, and a pharmaceutically acceptable carrier, as well as any desired excipients.

This invention further discloses a method of making a nanoparticulate megestrol composition according to the invention. Such a method comprises contacting megestrol particles and at least one surface stabilizer for a time and under conditions sufficient to provide a nanoparticulate megestrol composition. The one or more surface stabilizers can be contacted with megestrol either before, during, or after size reduction of the megestrol.

The present invention is also directed to methods of treatment using the nanoparticulate compositions of the invention for conditions such as endometriosis, dysmenorrhea, hirsutism, uterine bleeding, neoplastic diseases, methods of appetite enhancement, contraception, hormone replacement therapy, and treating patients following castration. Such methods comprises administering to a subject a therapeutically effective amount of a nanoparticulate megestrol composition according to the invention.

Finally, the present invention is directed to megestrol acetate compositions with improved physical (viscosity) and

pharmacokinetic profiles (such as less variability) over traditional forms of megestrol acetate.

Both the foregoing general description and the following detailed description are exemplary and explanatory and are intended to provide further explanation of the invention as claimed. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1**: Illustrates viscosity in units of mPa s as a function of concentration. Circles indicate the experimental values and the line illustrates the expected trend;

FIG. **2**: Illustrates viscosity in units of Pa s as a function of shear rate for two commercial samples, Bristol Myers Squibb and Par Pharmaceuticals, both at an active concentration of 40 mg/mL; and

FIG. **3**: Shows a photograph of, from left to right, a nanoparticulate dispersion of megestrol acetate, a commercial sample of megestrol acetate marketed by Par Pharmaceuticals, and a commercial sample of megestrol acetate marketed by Bristol Myers Squibb.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to nanoparticulate compositions comprising megestrol particles having an effective average particle size of less than about 2 microns. The compositions comprise megestrol and preferably at least one surface stabilizer associated with the surface of the drug.

As taught in the '684 patent, not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition. It was surprisingly discovered that stable nanoparticulate megestrol compositions can be made.

For example, nanoparticulate megestrol compositions with hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulfate (SLS) as surface stabilizers remained stable in an electrolyte solution mimicking the physiological pH of the stomach. Nanoparticulate megestrol compositions comprising HPMC and SLS are stable for several weeks at temperatures up to 40° C. with only minimal particle size growth. In addition, nanoparticulate megestrol compositions with hydroxypropylcellulose (HPC) and dioctyl sodium sulfosuccinate (DOSS) as surface stabilizers, HPMC and DOSS as surface stabilizers, polyvinylpyrrolidone (PVP) and DOSS as surface stabilizers, and Plasdone® S630 and DOSS as surface stabilizers were stable in electrolyte fluids and exhibited acceptable physical stability at 5° C. for 4 weeks. (Plasdone® S630 (ISP) is a random copolymer of vinyl acetate and vinyl pyrrolidone.) Moreover, the nanoparticulate megestrol/HPMC/SLS and nanoparticulate megestrol/HPMC/DOSS compositions also exhibited acceptable physical stability at 25° C. and 40° C. for 4 weeks.

Advantages of the nanoparticulate megestrol compositions of the invention include, but are not limited to: (1) low viscosity liquid nanoparticulate megestrol dosage forms; (2) for liquid nanoparticulate megestrol compositions having a low viscosity—better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (3) for liquid nanoparticulate megestrol compositions having a low viscosity—ease of dispensing because one can use a cup or a syringe; (4) faster onset of action; (5) smaller doses of megestrol required to obtain the same pharmacological effect as compared to conventional microcrystalline forms of megestrol; (6) increased bioavailability as compared to conventional microcrystalline forms of megestrol; (7) substantially similar pharmacokinetic profiles of the nanoparticulate megestrol compositions when administered in the fed versus the fasted state; (8) bioequivalency of the nanoparticulate megestrol compositions when administered in the fed versus the fasted state; (9) redispersibility of the nanoparticulate megestrol particles present in the compositions of the invention following administration; (10) bioadhesive nanoparticulate megestrol compositions; (11) improved pharmacokinetic profiles, such as more rapid megestrol absorption, greater megestrol absorption, and longer megestrol dose retention in the blood following administration; (12) the nanoparticulate megestrol compositions can be used in conjunction with other active agents; (13) the nanoparticulate megestrol compositions preferably exhibit an increased rate of dissolution as compared to conventional microcrystalline forms of megestrol; (14) improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller tablet or liquid dose volumes; (15) the nanoparticulate megestrol compositions are suitable for parenteral administration; (16) the nanoparticulate megestrol compositions can be sterile filtered; and (17) the nanoparticulate megestrol compositions do not require organic solvents or pH extremes.

The present invention is described herein using several definitions, as set forth below and throughout the application. "About" will be understood by persons of ordinary skill in the art and will vary to some extent on the context in which the term is used. If there are uses of the term which are not clear to persons of ordinary skill in the art given the context in which it is used, "about" will mean up to plus or minus 10% of the particular term.

As used herein with reference to stable drug particles, "stable" means that the megestrol particles do not appreciably flocculate or agglomerate due to interparticle attractive forces or otherwise increase in particle size.

"Conventional active agents or drugs" refers to non-nanoparticulate compositions of active agents or solubilized active agents or drugs. Non-nanoparticulate active agents have an effective average particle size of greater than about 2 microns.

A. Preferred Characteristics of the Nanoparticulate Megestrol Compositions of the Invention

1. Low Viscosity

Typical commercial formulations of megestrol, such as Megace®, are relatively large volume, highly viscous substances that are not well accepted by patient populations, particularly subjects suffering from wasting. "Wasting" is a condition in which a subject finds it difficult to eat because, for example, food makes the subject nauseous. A highly viscous medicine is not compatible with treating such a condition, as frequently the highly viscous substance can cause additional nausea.

Moreover, viscous solutions can be problematic in parenteral administration because these solutions require a slow syringe push and can stick to tubing. In addition, conventional formulations of poorly water-soluble active agents, such as megestrol, tend to be unsafe for intravenous administration techniques, which are used primarily in conjunction with highly water-soluble substances.

Liquid dosage forms of the nanoparticulate megestrol compositions of the invention provide significant advantages over conventional liquid megestrol dosage forms. The

low viscosity and silky texture of liquid dosage forms of the nanoparticulate megestrol compositions of the invention results in advantages in both preparation and use. These advantages include, for example: (1) better subject compliance due to the perception of a lighter formulation which is easier to consume and digest; (2) ease of dispensing because one can use a cup or a syringe; (3) potential for formulating a higher concentration of megestrol resulting in a smaller dosage volume and thus less volume for the subject to consume; and (4) easier overall formulation concerns.

Liquid megestrol dosage forms which are easier to consume are especially important when considering juvenile patients, terminally ill patients, and patients suffering from gastrointestinal tract dysfunction or other conditions where nausea and vomiting are symptoms. For example, patients suffering from cancer or AIDS-related complications are commonly hypermetabolic and, at various stages of disease, exhibit gastrointestinal dysfunction. Additionally, drugs used to treat these conditions often cause nausea and vomiting. Viscous or gritty formulations, and those that require a relatively large dosage volume, are not well tolerated by patient populations suffering from wasting associated with these diseases because the formulations can exacerbate nausea and encourage vomiting.

The viscosities of liquid dosage forms of nanoparticulate megestrol according to the invention are preferably less than about 1/200, less than about 1/175, less than about 1/150, less than about 1/125, less than about 1/100, less than about 1/75, less than about 1/50, or less than about 1/25 of existing commercial liquid oral megestrol acetate compositions, e.g. Megace®, at about the same concentration per ml of megestrol.

Typically the viscosity of liquid nanoparticulate megestrol dosage forms of the invention is from about 175 mPa s to about 1 mPa s, from about 150 mPa s to about 1 mPa, from about 125 mPa s to about 1 mPa s, from about 100 mPa s to about 1 mPa s, from about 75 mPa s to about 1 mPa s, from about 50 mPa s to about 1 mPa s, from about 25 mPa s to about 1 mPa s, from about 15 mPa s to about 1 mPa s, or from about 5 mPa s to about 1 mPa s. Such a viscosity is much more attractive for subject consumption and may lead to better overall subject compliance.

Viscosity is concentration and temperature dependent. Typically, a higher concentration results in a higher viscosity, while a higher temperature results in a lower viscosity. Viscosity as defined above refers to measurements taken at about 20° C. (The viscosity of water at 20° C. is 1 mPa s.) The invention encompasses equivalent viscosities measured at different temperatures.

A viscosity of 1.5 mPa s for a nanoparticulate megestrol dispersion having a concentration of 30 mg/mL, measured at 20° C., was obtained by the inventors. An equivalent viscosity at 4% active agent concentration would be 1.7 mPa s. Higher and lower viscosities can be obtained by varying the temperature and concentration of megestrol.

Another important aspect of the invention is that the nanoparticulate megestrol compositions of the invention are not turbid. "Turbid," as used herein refers to the property of particulate matter that can be seen with the naked eye or that which can be felt as "gritty." The nanoparticulate megestrol compositions of the invention can be poured out of or extracted from a container as easily as water, whereas a conventional standard commercial (i.e., non-nanoparticulate or solubilized) megestrol liquid dosage form exhibits notably more "sluggish" characteristics.

The liquid formulations of this invention can be formulated for dosages in any volume but preferably equivalent or smaller volumes than existing commercial formulations.

2. Fast Onset of Activity

The use of conventional formulations of megestrol is not ideal due to delayed onset of action. In contrast, the nanoparticulate megestrol compositions of the invention exhibit faster therapeutic effects.

Preferably, following administration the nanoparticulate megestrol compositions of the invention have a T_{max} of less than about 5 hours, less than about 4.5 hours, less than about 4 hours, less than about 3.5 hours, less than about 3 hours, less than about 2.75 hours, less than about 2.5 hours, less than about 2.25 hours, less than about 2 hours, less than about 1.75 hours, less than about 1.5 hours, less than about 1.25 hours, less than about 1.0 hours, less than about 50 minutes, less than about 40 minutes, less than about 30 minutes, less than about 25 minutes, less than about 20 minutes, less than about 15 minutes, or less than about 10 minutes.

3. Increased Bioavailability

The nanoparticulate megestrol compositions of the invention preferably exhibit increased bioavailability and require smaller doses as compared to prior conventional megestrol compositions administered at the same dose.

Any drug, including megestrol, can have adverse side effects. Thus, lower doses of megestrol which can achieve the same or better therapeutic effects as those observed with larger doses of conventional megestrol compositions are desired. Such lower doses can be realized with the nanoparticulate megestrol compositions of the invention because the greater bioavailability observed with the nanoparticulate megestrol compositions as compared to conventional drug formulations means that smaller does of drug are required to obtain the desired therapeutic effect. Specifically, a once a day dose of about 375 mg/5 mL (75 mg/mL) of a nanoparticulate megestrol acetate composition is considered equivalent to an 800 mg dose of Megace®.

Administration of nanoparticulate megestrol formulations of the present invention can exhibit bioavailability, as determined by AUC0-t, in an amount of about 3000 ng hr/ml to about 10,000 ng hr/ml, wherein C_{max} is about 300 ng/ml to about 1100 ng/ml in a fed human subject and AUC0-t in an amount of about 2000 ng hr/ml to about 9000 ng hr/ml, wherein C_{max} is about 300 ng/ml to about 2000 ng/ml in a fasted human subject. Preferably, nanoparticulate megestrol formulations of the present invention exhibit comparable bioavailability in a range of between about 75 and about 130%, more preferably between about 80% and about 125%, of the specified therapeutic parameter (e.g., AUC0-t or C_{max}).

4. The Pharmacokinetic Profiles of the Nanoparticulate Megestrol Compositions of the Invention are not Substantially Affected by the Fed or Fasted State of the Subject Ingesting the Compositions

The invention encompasses nanoparticulate megestrol compositions wherein the phannacokinetic profile of the megestrol is not substantially affected by the fed or fasted state of a subject ingesting the composition. This means that there is no substantial difference in the quantity of megestrol absorbed or the rate of megestrol absorption when the nanoparticulate megestrol compositions are administered in the fed versus the fasted state. Thus, the nanoparticulate megestrol compositions of the invention substantially eliminate the effect of food on the pharmacokinetics of megestrol.

The difference in absorption of the nanoparticulate megestrol composition of the invention, when administered in the fed versus the fasted state, is less than about 35%, less than about 30%, less than about 25%, less than about 20%, less

than about 15%, less than about 10%, less than about 5%, or less than about 3%. This is an especially important feature in treating patients with difficulty in maintaining a fed state.

In addition, preferably the difference in the rate of absorption (i.e., T_{max}) of the nanoparticulate megestrol compositions of the invention, when administered in the fed versus the fasted state, is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, less than about 3%, or essentially no difference.

Benefits of a dosage form which substantially eliminates the effect of food include an increase in subject convenience, thereby increasing subject compliance, as the subject does not need to ensure that they are taking a dose either with or without food.

5. Redispersibility Profiles of the Nanoparticulate Megestrol Compositions of the Invention

An additional feature of the nanoparticulate megestrol compositions of the invention is that the compositions redisperse such that the effective average particle size of the redispersed megestrol particles is less than about 2 microns. This is significant, as if upon administration the nanoparticulate megestrol particles present in the compositions of the invention did not redisperse to a substantially nanoparticulate particle size, then the dosage form may lose the benefits afforded by formulating megestrol into a nanoparticulate particle size.

This is because nanoparticulate megestrol compositions benefit from the small particle size of megestrol; if the nanoparticulate megestrol particles do not redisperse into the small particle sizes upon administration, then "clumps" or agglomerated megestrol particles are formed. With the formation of such agglomerated particles, the bioavailability of the dosage form may fall.

Preferably, the redispersed megestrol particles of the invention have an effective average particle size, by weight, of less than about 2 microns, less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

Moreover, the nanoparticulate megestrol compositions of the invention exhibit dramatic redispersion of the nanoparticulate megestrol particles upon administration to a mammal, such as a human or animal, as demonstrated by reconstitution in a biorelevant aqueous media. Such biorelevant aqueous media can be any aqueous media that exhibit the desired ionic strength and pH, which form the basis for the biorelevance of the media. The desired pH and ionic strength are those that are representative of physiological conditions found in the human body. Such biorelevant aqueous media can be, for example, aqueous electrolyte solutions or aqueous solutions of any salt, acid, or base, or a combination thereof, which exhibit the desired pH and ionic strength.

Biorelevant pH is well known in the art. For example, in the stomach, the pH ranges from slightly less than 2 (but typically greater than 1) up to 4 or 5. In the small intestine the pH can range from 4 to 6, and in the colon it can range from 6 to 8. Biorelevant ionic strength is also well known in the art. Fasted state gastric fluid has an ionic strength of about 0.1 M while fasted state intestinal fluid has an ionic strength of about 0.14. See e.g., Lindahl et al., "Characterization of Fluids from the Stomach and Proximal Jejunum in Men and Women," *Pharm. Res.*, 14 (4): 497–502 (1997).

It is believed that the pH and ionic strength of the test solution is more critical than the specific chemical content. Accordingly, appropriate pH and ionic strength values can be obtained through numerous combinations of strong acids, strong bases, salts, single or multiple conjugate acid-base pairs (i.e., weak acids and corresponding salts of that acid), monoprotic and polyprotic electrolytes, etc.

Representative electrolyte solutions can be, but are not limited to, HCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and NaCl solutions, ranging in concentration from about 0.001 to about 0.1 M, and mixtures thereof. For example, electrolyte solutions can be, but are not limited to, about 0.1 M HCl or less, about 0.01 M HCl or less, about 0.001 M HCl or less, about 0.1 M NaCl or less, about 0.01 M NaCl or less, about 0.001 M NaCl or less, and mixtures thereof. Of these electrolyte solutions, 0.01 M HCl and/or 0.1 M NaCl, are most representative of fasted human physiological conditions, owing to the pH and ionic strength conditions of the proximal gastrointestinal tract.

Electrolyte concentrations of 0.001 M HCl, 0.01 M HCl, and 0.1 M HCl correspond to pH 3, pH 2, and pH 1, respectively. Thus, a 0.01 M HCl solution simulates typical acidic conditions found in the stomach. A solution of 0.1 M NaCl provides a reasonable approximation of the ionic strength conditions found throughout the body, including the gastrointestinal fluids, although concentrations higher than 0.1 M may be employed to simulate fed conditions within the human GI tract.

Exemplary solutions of salts, acids, bases or combinations thereof, which exhibit the desired pH and ionic strength, include but are not limited to phosphoric acid/phosphate salts+sodium, potassium and calcium salts of chloride, acetic acid/acetate salts+sodium, potassium and calcium salts of chloride, carbonic acid/bicarbonate salts+sodium, potassium and calcium salts of chloride, and citric acid/citrate salts+sodium, potassium and calcium salts of chloride.

6. Bioadhesive Nanoparticulate Megestrol Compositions

Bioadhesive nanoparticulate megestrol compositions of the invention comprise at least one cationic surface stabilizer, which are described in more detail below. Bioadhesive formulations of megestrol exhibit exceptional bioadhesion to biological surfaces, such as mucous.

In the case of bioadhesive nanoparticulate megestrol compositions, the term "bioadhesion" is used to describe the adhesion between the nanoparticulate megestrol compositions and a biological substrate (i.e. gastrointestinal mucin, lung tissue, nasal mucosa, etc.). See e.g., U.S. Pat. No. 6,428,814 for "Bioadhesive Nanoparticulate Compositions Having Cationic Surface Stabilizers," which is specifically incorporated by reference.

The bioadhesive megestrol compositions of the invention are useful in any situation in which it is desirable to apply the compositions to a biological surface. The bioadhesive megestrol compositions coat the targeted surface in a continuous and uniform film which is invisible to the naked human eye.

A bioadhesive nanoparticulate megestrol composition slows the transit of the composition, and some megestrol particles would also most likely adhere to tissue other than

the mucous cells and therefore give a prolonged exposure to megestrol, thereby increasing absorption and the bioavailability of the administered dosage.

7. Pharmacokinetic Profiles of the Nanoparticulate Megestrol Compositions of the Invention

The present invention also provides compositions of nanoparticulate megestrol having a desirable pharmacokinetic profile when administered to mammalian subjects. The desirable pharmacokinetic profile of the nanoparticulate megestrol compositions comprise the parameters: (1) that the T_{max} of megestrol, when assayed in the plasma of the mammalian subject, is less than about 5 hours; and (2) a C_{max} of megestrol is greater than about 30 ng/ml. Preferably, the T_{max} parameter of the pharmacokinetic profile is not greater than about 3 hours. Most preferably, the T_{max} parameter of the pharmacokinetic profile is not greater than about 2 hours.

The desirable pharmacokinetic profile, as used herein, is the pharmacokinetic profile measured after the initial dose of megestrol. For example, in a subject receiving 40 mg of megestrol four times a day, the T_{max} and C_{max} after the initial dose must be less than about 5 hours and greater than about 30 ng/ml, respectively. The compositions can be formulated in any way as described below.

Current formulations of megestrol include oral suspensions and tablets. According to the package insert of Megace®, the pharmacokinetic profile of the oral suspension contains parameters such that the median T_{max} is 5 hours and the mean C_{max} is 753 ng/ml. Further, the T_{max} and C_{max} for the Megace® 40 mg tablet, after the initial dose, is 2.2 hours and 27.6 ng/ml, respectively. *Physicians Desk Reference,* 55th Ed., 2001. The nanoparticulate megestrol compositions of the invention simultaneously improve upon at least the T_{max} and C_{max} parameters of the pharmacokinetic profile of megestrol.

In one embodiment, a threshold blood plasma concentration of megestrol of about 700 ng/ml is attained in less than about 5 hours after administration of the formulation, and preferably not greater than about 3 hours.

Preferably, the T_{max} of an administered dose of a nanoparticulate megestrol composition is less than that of a conventional standard commercial non-nanoparticulate megestrol composition, administered at the same dosage. In addition, preferably the C_{max} of a nanoparticulate megestrol composition is greater than the C_{max} of a conventional standard commercial non-nanoparticulate megestrol composition, administered at the same dosage.

A preferred nanoparticulate megestrol composition of the invention exhibits in comparative pharmacokinetic testing with a standard commercial formulation of megestrol, such as Megace® oral suspension or tablet from Bristol Myers Squibb, a T_{max} which is less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, or less than about 10% of the T_{max} exhibited by the standard commercial formulation of megestrol.

A preferred nanoparticulate megestrol composition of the invention exhibits in comparative pharmacokinetic testing with a standard commercial formulation of megestrol, such as Megace® oral suspension or tablet from Bristol Myers Squibb, a C_{max} which is greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, or greater than about 150% than the C_{max} exhibited by the standard commercial formulation of megestrol.

There is no critical upper limit of blood plasma concentration so long as the dosage amounts set out below are not significantly exceeded. A suitable dose of megestrol, administered according to the method of the invention, is typically in the range of about 1 mg/day to about 1000 mg/day, or from about 40 mg/day to about 800 mg/day. Preferably, the therapeutically effective amount of the nanoparticulate megestrol compositions of the invention is ⅙, ⅕, ¼, ⅓rd, or ½ of the therapeutically effective amount of existing commercial megestrol formulations.

Any standard pharmacokinetic protocol can be used to determine blood plasma concentration profile in humans following administration of a nanoparticulate megestrol composition, and thereby establish whether that composition meets the pharmacokinetic criteria set out herein. For example, a randomized single-dose crossover study can be performed using a group of healthy adult human subjects. The number of subjects should be sufficient to provide adequate control of variation in a statistical analysis, and is typically about 10 or greater, although for certain purposes a smaller group can suffice. Each subject receives by oral administration at time zero a single dose (e.g., 300 mg) of a test formulation of megestrol, normally at around 8 am following an overnight fast. The subjects continue to fast and remain in an upright position for about 4 hours after administration of the megestrol formulation. Blood samples are collected from each subject prior to administration (e.g., 15 minutes) and at several intervals after administration. For the present purpose it is preferred to take several samples within the first hour, and to sample less frequently thereafter. Illustratively, blood samples could be collected at 15, 30, 45, 60, and 90 minutes after administration, then every hour from 2 to 10 hours after administration. Additional blood samples may also be taken later, for example at 12 and 24 hours after administration. If the same subjects are to be used for study of a second test formulation, a period of at least 7 days should elapse before administration of the second formulation. Plasma is separated from the blood samples by centrifugation and the separated plasma is analyzed for megestrol by a validated high performance liquid chromatography (HPLC) procedure, such as for example Garver et al., *J. Pharm. Sci.* 74(6):664–667 (1985), the entirety of which is hereby incorporated by reference. Plasma concentrations of megestrol referenced herein are intended to mean total megestrol concentrations including both free and bound megestrol.

Any formulation giving the desired pharmacokinetic profile is suitable for administration according to the present methods. Exemplary types of formulations giving such profiles are liquid dispersions and solid dose forms of nanoparticulate megestrol. Dispersions of megestrol have proven to be stable at temperatures up to 50° C. If the liquid dispersion medium is one in which the nanoparticulate megestrol has very low solubility, the nanoparticulate megestrol particles are present as suspended particles. The smaller the megestrol particles, the higher the probability that the formulation will exhibit the desired pharmacokinetic profile.

8. Combination Pharmacokinetic Profile Compositions

In yet another embodiment of the invention, a first nanoparticulate megestrol composition providing a desired pharmacokinetic profile is co-administered, sequentially admin-

istered, or combined with at least one other megestrol composition that generates a desired different pharmacokinetic profile. More than two megestrol compositions can be co-administered, sequentially administered, or combined. While the first megestrol composition has a nanoparticulate particle size, the additional one or more megestrol compositions can be nanoparticulate, solubilized, or have a conventional microparticulate particle size.

For example, a first megestrol composition can have a nanoparticulate particle size, conferring a short T_{max} and typically a higher C_{max}. This first megestrol composition can be combined, co-administered, or sequentially administered with a second composition comprising: (1) megestrol having a larger (but still nanoparticulate as defined herein) particle size, and therefore exhibiting slower absorption, a longer T_{max}, and typically a lower C_{max}; or (2) a microparticulate or solubilized megestrol composition, exhibiting a longer T_{max}, and typically a lower C_{max}.

The second, third, fourth, etc., megestrol compositions can differ from the first, and from each other, for example: (1) in the effective average particle sizes of megestrol; or (2) in the dosage of megestrol. Such a combination composition can reduce the dose frequency required.

If the second megestrol composition has a nanoparticulate particle size, then preferably the megestrol particles of the second composition have at least one surface stabilizer associated with the surface of the drug particles. The one or more surface stabilizers can be the same as or different from the surface stabilizer(s) present in the first megestrol composition.

Preferably where co-administration of a "fast-acting" formulation and a "longer-lasting" formulation is desired, the two formulations are combined within a single composition, for example a dual-release composition.

9. Combination Active Agent Compositions

The invention encompasses the nanoparticulate megestrol compositions of the invention formulated or co-administered with one or more non-megestrol active agents, which are either conventional (solubilized or microparticulate) or nanoparticulate. Methods of using such combination compositions are also encompassed by the invention. The non-megestrol active agents can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

The compound to be administered in combination with a nanoparticulate megestrol composition of the invention can be formulated separately from the nanoparticulate megestrol composition or co-formulated with the nanoparticulate megestrol composition. Where a nanoparticulate megestrol composition is co-formulated with a second active agent, the second active agent can be formulated in any suitable manner, such as immediate-release, rapid-onset, sustained-release, or dual-release form.

If the non-megestrol active agent has a nanoparticulate particle size i.e., a particle size of less than about 2 microns, then preferably it will have one or more surface stabilizers associated with the surface of the active agent. In addition, if the active agent has a nanoparticulate particle size, then it is preferably poorly soluble and dispersible in at least one liquid dispersion media. By "poorly soluble" it is meant that the active agent has a solubility in a liquid dispersion media of less than about 30 mg/mL, less than about 20 mg/mL, less than about 10 mg/mL, or less than about 1 mg/mL. Useful liquid dispersion medias include, but are not limited to, water, aqueous salt solutions, safflower oil, and solvents such as ethanol, t-butanol, hexane, and glycol.

Such non-megestrol active agents can be, for example, a therapeutic agent. A therapeutic agent can be a pharmaceutical agent, including biologics. The active agent can be selected from a variety of known classes of drugs, including, for example, amino acids, proteins, peptides, nucleotides, anti-obesity drugs, central nervous system stimulants, carotenoids, corticosteroids, elastase inhibitors, anti-fungals, oncology therapies, anti-emetics, analgesics, cardiovascular agents, anti-inflammatory agents, such as NSAIDs and COX-2 inhibitors, anthelmintics, anti-arrhythmic agents, antibiotics (including penicillins), anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobacterial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytics, sedatives (hypnotics and neuroleptics), astringents, alpha-adrenergic receptor blocking agents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, contrast media, corticosteroids, cough suppressants (expectorants and mucolytics), diagnostic agents, diagnostic imaging agents, diuretics, dopaminergics (anti-parkinsonian agents), haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radio-pharmaceuticals, sex hormones (including steroids), anti-allergic agents, stimulants and anoretics, sympathomimetics, thyroid agents, vasodilators, and xanthines.

A description of these classes of active agents and a listing of species within each class can be found in Martindale's *The Extra Pharmacopoeia,* 31st Edition (The Pharmaceutical Press, London, 1996), specifically incorporated by reference. The active agents are commercially available and/or can be prepared by techniques known in the art.

Exemplary nutraceuticals and dietary supplements are disclosed, for example, in Roberts et al., *Nutraceuticals: The Complete Encyclopedia of Supplements, Herbs, Vitamins, and Healing Foods* (American Nutraceutical Association, 2001), which is specifically incorporated by reference. Dietary supplements and nutraceuticals are also disclosed in *Physicians' Desk Reference for Nutritional Supplements,* 1st Ed. (2001) and *The Physicians' Desk Reference for Herbal Medicines,* 1st Ed. (2001), both of which are also incorporated by reference. A nutraceutical or dietary supplement, also known as a phytochemical or functional food, is generally any one of a class of dietary supplements, vitamins, minerals, herbs, or healing foods that have medical or pharmaceutical effects on the body.

Exemplary nutraceuticals or dietary supplements include, but are not limited to, lutein, folic acid, fatty acids (e.g., DHA and ARA), fruit and vegetable extracts, vitamin and mineral supplements, phosphatidylserine, lipoic acid, melatonin, glucosamine/chondroitin, Aloe Vera, Guggul, glutamine, amino acids (e.g., arginine, iso-leucine, leucine, lysine, methionine, phenylanine, threonine, tryptophan, and valine), green tea, lycopene, whole foods, food additives, herbs, phytonutrients, antioxidants, flavonoid constituents of fruits, evening primrose oil, flax seeds, fish and marine animal oils, and probiotics. Nutraceuticals and dietary supplements also include bio-engineered foods genetically engineered to have a desired property, also known as "pharmafoods."

10. Sterile Filtered Nanoparticulate Megestrol Compositions

The nanoparticulate megestrol compositions of the invention can be sterile filtered. This obviates the need for heat sterilization, which can harm or degrade megestrol, as well as result in crystal growth and particle aggregation.

Sterile filtration can be difficult because of the required small particle size of the composition. Filtration is an effective method for sterilizing homogeneous solutions when the membrane filter pore size is less than or equal to about 0.2 microns (200 nm) because a 0.2 micron filter is sufficient to remove essentially all bacteria. Sterile filtration is normally not used to sterilize conventional suspensions of micron-sized megestrol because the megestrol particles are too large to pass through the membrane pores.

A sterile nanoparticulate megestrol dosage form is particularly useful in treating immunocompromised patients, infants or juvenile patients, and the elderly, as these patient groups are the most susceptible to infection caused by a non-sterile liquid dosage form.

Because the nanoparticulate megestrol compositions of the invention can be sterile filtered, and because the compositions can have a very small megestrol effective average particle size, the compositions are suitable for parenteral administration.

11. Miscellaneous Benefits of the Nanoparticulate Megestrol Compositions of the Invention

The nanoparticulate megestrol compositions preferably exhibit an increased rate of dissolution as compared to conventional microcrystalline forms of megestrol. In addition, the compositions of the invention exhibit improved performance characteristics for oral, intravenous, subcutaneous, or intramuscular injection, such as higher dose loading and smaller tablet or liquid dose volumes. Moreover, the nanoparticulate megestrol compositions of the invention do not require organic solvents or pH extremes.

Another benefit of the nanoparticulate megestrol compositions of the invention is that is was surprisingly discovered that upon administration, nanoparticulate compositions of megestrol acetate reach therapeutic blood levels within one dose. This is in dramatic contrast to the current commercially available megestrol acetate composition (Megace® by Bristol Myers Squibb Co.), which requires multiple doses, administered over several days to a week, to build up to a therapeutic level of drug in the blood stream.

B. Compositions The invention provides compositions comprising nanoparticulate megestrol particles and preferably at least one surface stabilizer. The one or more surface stabilizers are preferably associated with the surface of the megestrol particles. Surface stabilizers useful herein preferably do not chemically react with the megestrol particles or itself. Individual molecules of the surface stabilizer are essentially free of intermolecular cross-linkages.

The present invention also includes nanoparticulate megestrol compositions together with one or more non-toxic physiologically acceptable carriers, adjuvants, or vehicles, collectively referred to as carriers. The compositions can be formulated for parenteral injection (e.g., intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracistemal, intraperitoneal, or topical administration, and the like.

1. Megestrol Particles

As used herein the term megestrol, which is the active ingredient in the composition, is used to mean megestrol, megestrol acetate (17α-acetyloxy-6-methylpregna-4,6-diene-3,20-dione), or a salt thereof. The megestrol particles can be present in a crystalline phase, an amorphous phase, a semi-crystalline phase, a semi-amorphous phase, or a mixture thereof.

Megestrol acetate is well known in the art and is readily recognized by one of ordinary skill. Generally, megestrol is used for treating breast cancer, endometrial cancer and, less frequently, prostate cancer. Megestrol is also frequently used as an appetite stimulant for patients in a wasting state, such as HIV wasting, cancer wasting, and anorexia. Megestrol may be used for other indications where progestins are typically used, such as hormone replacement therapy in post-menopausal women and oral contraception. Further, megestrol may be used for ovarian suppression in several conditions such as endometriosis, hirsutism, dysmenorrhea, and uterine bleeding, as well as uterine cancer, cervical cancer, and renal cancer. Megestrol is also used in patients following castration.

2. Surface Stabilizers

The choice of a surface stabilizer for megestrol is non-trivial. Accordingly, the present invention is directed to the surprising discovery that nanoparticulate megestrol compositions can be made.

Combinations of more than one surface stabilizer can be used in the invention. Preferred surface stabilizers include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, random copolymers of vinyl pyrrolidone and vinyl acetate, sodium lauryl sulfate, dioctylsulfosuccinate or a combination thereof. Preferred primary surface stabilizers include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, random copolymers of vinyl pyrrolidone and vinyl acetate, or a combination thereof. Preferred secondary surface stabilizers include, but are not limited to, sodium lauryl sulfate and dioctylsulfosuccinate.

Other surface stabilizers which can be employed in the invention include, but are not limited to, known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products, and surfactants. Surface stabilizers include nonionic, cationic, ionic, and zwitterionic surfactants.

Representative examples of surface stabilizers include hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin (phosphatides), dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers (e.g., macrogol ethers such as cetomacrogol 1000), polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters (e.g., the commercially available Tweens such as e.g., Tween 20® and Tween 80® (ICI Speciality Chemicals)); polyethylene glycols (e.g., Carbowaxs 3550® and 934® (Union Carbide)), polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde (also known as tyloxapol, superione, and triton), poloxamers (e.g., Pluronics F68® and F108®, which are block copolymers of ethylene oxide and propylene oxide); poloxamines (e.g., Tetronic 908®, also known as Poloxamine 908®, which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine (BASF Wyandotte Corporation, Parsippany, N.J.)); Tetronic 1508® (T-1508) (BASF Wyandotte Corporation),

Tritons X-200®, which is an alkyl aryl polyether sulfonate (Rohm and Haas); Crodestas F-110®, which is a mixture of sucrose stearate and sucrose distearate (Croda Inc.); p-isononylphenoxypoly-(glycidol), also known as Olin-10G® or Surfactant 10-G® (Olin Chemicals, Stamford, Conn.); Crodestas SL-40® (Croda, Inc.); and SA9OHCO, which is $C_{18}H_{37}CH_2(CON(CH_3)—CH_2(CHOH)_4(CH_2OH)_2$ (Eastman Kodak Co.); decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, and the like.

Examples of useful cationic surface stabilizers include, but are not limited to, polymers, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, and nonpolymeric compounds, such as zwitterionic stabilizers, poly-n-methylpyridinium, anthryul pyridinium chloride, cationic phospholipids, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammonium-bromide bromide (PMMTMABr), hexyldesyltrimethylammonium bromide (HDMAB), and polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate.

Other useful cationic stabilizers include, but are not limited to, cationic lipids, sulfonium, phosphonium, and quarternary ammonium compounds, such as stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15}dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzene-alkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride (ALIQUAT 336™), POLYQUAT 10™, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters (such as choline esters of fatty acids), benzalkonium chloride, stearalkonium chloride compounds (such as stearyltrimonium chloride and Di-stearyldimonium chloride), cetyl pyridinium bromide or chloride, halide salts of quaternized polyoxyethylalkylamines, MIRAPOL™ and ALKAQUAT™ (Alkaril Chemical Company), alkyl pyridinium salts; amines, such as alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, and vinyl pyridine, amine salts, such as lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, and alkylimidazolium salt, and amine oxides; imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, such as poly[diallyl dimethylammonium chloride] and poly-[N-methyl vinyl pyridinium chloride]; and cationic guar.

Such exemplary cationic surface stabilizers and other useful cationic surface stabilizers are described in J. Cross and E. Singer, *Cationic Surfactants: Analytical and Biological Evaluation* (Marcel Dekker, 1994); P. and D. Rubingh (Editor), *Cationic Surfactants: Physical Chemistry* (Marcel Dekker, 1991); and J. Richmond, *Cationic Surfactants: Organic Chemistry,* (Marcel Dekker, 1990).

Particularly preferred nonpolymeric primary stabilizers are any nonpolymeric compound, such benzalkonium chloride, a carbonium compound, a phosphonium compound, an oxonium compound, a halonium compound, a cationic organometallic compound, a quarternary phosphorous compound, a pyridinium compound, an anilinium compound, an ammonium compound, a hydroxylammonium compound, a primary ammonium compound, a secondary ammonium compound, a tertiary ammonium compound, and quarternary ammonium compounds of the formula $NR_1R_2R_3R_4^{(+)}$. For compounds of the formula $NR_1R_2R_3R_4^{(+)}$:

(i) none of R_1R_4 are CH_3;
(ii) one of R_1–R_4 is CH_3;
(iii) three of R_1–R_4 are CH_3;
(iv) all of R_1–R_4 are CH_3;
(v) two of R_1–R_4 are CH_3, one of R_1–R_4 is $C_6H_5CH_2$, and one of R_1–R_4 is an alkyl chain of seven carbon atoms or less;
(vi) two of R_1–R_4 are CH_3, one of R_1–R_4 is $C_6H_5CH_2$, and one of R_1–R_4 is an alkyl chain of nineteen carbon atoms or more;
(vii) two of R_1–R_4 are CH_3 and one of R_1–R_4 is the group $C_6H_5(CH_2)_n$, where n>1;
(viii) two of R_1–R_4 are CH_3, one of R_1–R_4 is $C_6H_5CH_2$, and one of R_1–R_4 comprises at least one heteroatom;
(ix) two of R_1–R_4 are CH_3, one of R_1–R_4 is $C_6H_5CH_2$, and one of R_1–R_4 comprises at least one halogen;
(x) two of R_1–R_4 are CH_3, one of R_1–R_4 is $C_6H_5CH_2$, and one of R_1–R_4 comprises at least one cyclic fragment;
(xi) two of R_1–R_4 are CH_3 and one of R_1–R_4 is a phenyl ring; or
(xii) two of R_1–R_4 are CH_3 and two of R_1–R_4 are purely aliphatic fragments.

Such compounds include, but are not limited to, behenalkonium chloride, benzethonium chloride, cetylpyridinium chloride, behentrimonium chloride, lauralkonium chloride, cetalkonium chloride, cetrimonium bromide, cetrimonium chloride, cethylamine hydrofluoride, chlorallylmethenamine chloride (Quaternium-15), distearyldimonium chloride (Quaternium-5), dodecyl dimethyl ethylbenzyl ammonium chloride(Quaternium-14), Quaternium-22, Quaternium-26, Quaternium-18 hectorite, dimethylaminoethylchloride hydrochloride, cysteine hydrochloride, diethanolammonium POE (10) oletyl ether phosphate, diethanolammonium POE (3)oleyl ether phosphate, tallow alkonium

chloride, dimethyl dioctadecylammoniumbentonite, stearalkonium chloride, domiphen bromide, denatonium benzoate, myristalkonium chloride, laurtrimonium chloride, ethylenediamine dihydrochloride, guanidine hydrochloride, pyridoxine HCl, iofetamine hydrochloride, meglumine hydrochloride, methylbenzethonium chloride, myrtrimonium bromide, oleyltrimonium chloride, polyquaternium-1, procainehydrochloride, cocobetaine, stearalkonium bentonite, stearalkoniumhectonite, stearyl trihydroxyethyl propylenediamine dihydrofluoride, tallowtrimonium chloride, and hexadecyltrimethyl ammonium bromide.

Most of these surface stabilizers are known pharmaceutical excipients and are described in detail in the *Handbook of Pharmaceutical Excipients*, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain (The Pharmaceutical Press, 2000), specifically incorporated by reference. The surface stabilizers are commercially available and/or can be prepared by techniques known in the art.

3. Other Pharmaceutical Excipients

Pharmaceutical megestrol compositions according to the invention may also comprise one or more binding agents, filling agents, lubricating agents, suspending agents, sweeteners, flavoring agents, preservatives, buffers, wetting agents, disintegrants, effervescent agents, and other excipients. Such excipients are known in the art.

Examples of filling agents are lactose monohydrate, lactose anhydrous, and various starches; examples of binding agents are various celluloses and cross-linked polyvinylpyrrolidone, microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102, microcrystalline cellulose, and silicified microcrystalline cellulose (ProSolv SMCC™).

Suitable lubricants, including agents that act on the flowability of the powder to be compressed, are colloidal silicon dioxide, such as Aerosil® 200, talc, stearic acid, magnesium stearate, calcium stearate, and silica gel.

Examples of sweeteners are any natural or artificial sweetener, such as sucrose, xylitol, sodium saccharin, cyclamate, aspartame, and acsulfame. Examples of flavoring agents are Magnasweet® (trademark of MAFCO), bubble gum flavor, and fruit flavors, and the like.

Examples of preservatives are potassium sorbate, methylparaben, propylparaben, benzoic acid and its salts, other esters of parahydroxybenzoic acid such as butylparaben, alcohols such as ethyl or benzyl alcohol, phenolic compounds such as phenol, or quarternary compounds such as benzalkonium chloride.

Suitable diluents include pharmaceutically acceptable inert fillers, such as microcrystalline cellulose, lactose, dibasic calcium phosphate, saccharides, and/or mixtures of any of the foregoing. Examples of diluents include microcrystalline cellulose, such as Avicel® PH101 and Avicel® PH102; lactose such as lactose monohydrate, lactose anhydrous, and Pharmatose® DCL21; dibasic calcium phosphate such as Emcompress®; mannitol; starch; sorbitol; sucrose; and glucose.

Suitable disintegrants include lightly crosslinked polyvinyl pyrrolidone, corn starch, potato starch, maize starch, and modified starches, croscarmellose sodium, cross-povidone, sodium starch glycolate, and mixtures thereof.

Examples of effervescent agents are effervescent couples such as an organic acid and a carbonate or bicarbonate. Suitable organic acids include, for example, citric, tartaric, malic, fumaric, adipic, succinic, and alginic acids and anhydrides and acid salts. Suitable carbonates and bicarbonates include, for example, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, magnesium carbonate, sodium glycine carbonate, L-lysine carbonate, and arginine carbonate. Alternatively, only the sodium bicarbonate component of the effervescent couple may be present.

4. Nanoparticulate Megestrol or Active Agent Particle Size

As used herein, particle size is determined on the basis of the weight average particle size as measured by conventional particle size measuring techniques well known to those skilled in the art. Such techniques include, for example, sedimentation field flow fractionation, photon correlation spectroscopy, light scattering, and disk centrifugation.

The compositions of the invention comprise nanoparticulate megestrol particles which have an effective average particle size of less than about 2000 nm (i.e., 2 microns). In other embodiments of the invention, the megestrol particles have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, when measured by the above techniques.

If the nanoparticulate megestrol composition additionally comprises one or more non-megestrol nanoparticulate active agents, then such active agents have an effective average particle size of less than about 2000 nm (i.e., 2 microns). In other embodiments of the invention, the nanoparticulate non-megestrol active agents can have an effective average particle size of less than about 1900 nm, less than about 1800 nm, less than about 1700 nm, less than about 1600 nm, less than about 1500 nm, less than about 1400 nm, less than about 1300 nm, less than about 1200 nm, less than about 1100 nm, less than about 1000 nm, less than about 900 nm, less than about 800 nm, less than about 700 nm, less than about 600 nm, less than about 500 nm, less than about 400 nm, less than about 300 nm, less than about 250 nm, less than about 200 nm, less than about 150 nm, less than about 100 nm, less than about 75 nm, or less than about 50 nm, as measured by light-scattering methods, microscopy, or other appropriate methods.

By "an effective average particle size of less than about 2000 nm" it is meant that at least 50% of the nanoparticulate megestrol or nanoparticulate non-megestrol active agent particles have a particle size of less than about 2000 nm, by weight, when measured by the above-noted techniques. Preferably, at least about 70%, about 90%, about 95%, or about 99% of the nanoparticulate megestrol or nanoparticulate non-megestrol active agent particles have a particle size of less than the effective average, i.e., less than about 2000 nm, less than about 1900 nm, less than about 1800 nm, etc.

If the nanoparticulate megestrol composition is combined with a conventional or microparticulate megestrol composition or non-megestrol active agent composition, then such a composition is either solubilized or has an effective average particle size of greater than about 2 microns. By "an effective average particle size of greater than about 2 microns" it is meant that at least 50% of the conventional megestrol or non-megestrol active agent particles have a particle size of greater than about 2 microns, by weight,

when measured by the above-noted techniques. In other embodiments of the invention, at least about 70%, about 90%, about 95%, or about 99% of the conventional megestrol or non-megestrol active agent particles have a particle size greater than about 2 microns.

5. Concentration of Nanoparticulate Megestrol and Surface Stabilizers

The relative amounts of nanoparticulate megestrol and one or more surface stabilizers can vary widely. The optimal amount of the individual components can depend, for example, the hydrophilic lipophilic balance (HLB), melting point, and the surface tension of water solutions of the stabilizer, etc.

The concentration of megestrol can vary from about 99.5% to about 0.001%, from about 95% to about 0.1%, or from about 90% to about 0.5%, by weight, based on the total combined dry weight of the megestrol and at least one surface stabilizer, not including other excipients.

The concentration of the at least one surface stabilizer can vary from about 0.5% to about 99.999%, from about 5.0% to about 99.9%, or from about 10% to about 99.5%, by weight, based on the total combined dry weight of the megestrol and at least one surface stabilizer, not including other excipients.

If a combination of two or more surface stabilizers is employed in the composition, the concentration of the at least one primary surface stabilizer can vary from about 0.01% to about 99.5%, from about 0.1% to about 95%, or from about 0.5% to about 90%, by weight, based on the total combined dry weight of the megestrol, at least one primary surface stabilizer, and at least one secondary surface stabilizer, not including other excipients. In addition, the concentration of the at least one secondary surface stabilizer can vary from about 0.01% to about 99.5%, from about 0.1% to about 95%, or from about 0.5% to about 90%, by weight, based on the total combined dry weight of the megestrol, at least one primary surface stabilizer, and at least one secondary surface stabilizer, not including other excipients.

C. Methods of Making Nanoparticulate Megestrol Compositions

The nanoparticulate megestrol compositions can be made using, for example, milling, homogenization, or precipitation techniques. Exemplary methods of making nanoparticulate compositions are described in the '684 patent.

Methods of making nanoparticulate compositions are also described in U.S. Pat. No. 5,518,187 for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,718,388 for "Continuous Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,862,999 for "Method of Grinding Pharmaceutical Substances;" U.S. Pat. No. 5,665,331 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Pat. No. 5,662,883 for "Co-Microprecipitation of Nanoparticulate Pharmaceutical Agents with Crystal Growth Modifiers;" U.S. Pat. No. 5,560,932 for "Microprecipitation of Nanoparticulate Pharmaceutical Agents;" U.S. Pat. No. 5,543,133 for "Process of Preparing X-Ray Contrast Compositions Containing Nanoparticles;" U.S. Pat. No. 5,534,270 for "Method of Preparing Stable Drug Nanoparticles;" U.S. Pat. No. 5,510,118 for "Process of Preparing Therapeutic Compositions Containing Nanoparticles;" and U.S. Pat. No. 5,470,583 for "Method of Preparing Nanoparticle Compositions Containing Charged Phospholipids to Reduce Aggregation," all of which are specifically incorporated by reference.

The resultant nanoparticulate megestrol compositions can be utilized in solid or liquid dosage formulations, such as controlled release formulations, solid dose fast melt formulations, aerosol formulations, lyophilized formulations, tablets, capsules, etc.

1. Milling to Obtain Nanoparticulate Megestrol Dispersions

Milling megestrol to obtain a nanoparticulate megestrol dispersion comprises dispersing megestrol particles in a liquid dispersion medium in which megestrol is poorly soluble, followed by applying mechanical means in the presence of grinding media to reduce the particle size of megestrol to the desired effective average particle size. The dispersion medium can be, for example, water, safflower oil, ethanol, t-butanol, glycerin, polyethylene glycol (PEG), hexane, or glycol.

The megestrol particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the megestrol particles can be contacted with one or more surface stabilizers after attrition. Other compounds, such as a diluent, can be added to the megestrol/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

2. Precipitation to Obtain Nanoparticulate Megestrol Compositions

Another method of forming the desired nanoparticulate megestrol composition is by microprecipitation. This is a method of preparing stable dispersions of poorly soluble active agents in the presence of one or more surface stabilizers and one or more colloid stability enhancing surface active agents free of any trace toxic solvents or solubilized heavy metal impurities. Such a method comprises, for example: (1) dissolving megestrol in a suitable solvent; (2) adding the formulation from step (1) to a solution comprising at least one surface stabilizer; and (3) precipitating the formulation from step (2) using an appropriate non-solvent. The method can be followed by removal of any formed salt, if present, by dialysis or diafiltration and concentration of the dispersion by conventional means.

3. Homogenization to Obtain_Nanoparticulate Megestrol Compositions

Exemplary homogenization methods of preparing nanoparticulate active agent compositions are described in U.S. Pat. No. 5,510,118, for "Process of Preparing Therapeutic Compositions Containing Nanoparticles."

Such a method comprises dispersing megestrol particles in a liquid dispersion medium, followed by subjecting the dispersion to homogenization to reduce the particle size of the megestrol to the desired effective average particle size. The megestrol particles can be reduced in size in the presence of at least one surface stabilizer. Alternatively, the megestrol particles can be contacted with one or more surface stabilizers either before or after attrition. Other compounds, such as a diluent, can be added to the megestrol/surface stabilizer composition either before, during, or after the size reduction process. Dispersions can be manufactured continuously or in a batch mode.

D. Methods of Using Nanoparticulate Megestrol Formulations of the Invention

1. Applications of the Nanoparticulate Compositions of the Invention

The nanoparticulate megestrol compositions of the invention may be used as an appetite stimulant to treat wasting conditions or cachexia. As used herein, the term "wasting"

is used to mean a condition where the patient is losing body mass as a side effect of a disease progression, a disease treatment, or other condition. Examples of conditions where wasting is prevalent include, but are not limited to, HIV or AIDS, cancer, cachexia and anorexia.

Additional conditions where the nanoparticulate megestrol compositions of the invention may be used include, but are not limited to, neoplastic diseases where the disease normally regresses or the patient's symptoms are normally reduced in response to megestrol, or any other progestin.

The nanoparticulate megestrol compositions of the invention may also be used to treat conditions such as breast cancer, endometrial cancer, uterine cancer, cervical cancer, prostate cancer, and renal cancer. As used herein, the term "cancer" is used as one of ordinary skill in the art would recognize the term. Examples of cancers include, but are not limited to, neoplasias (or neoplasms), hyperplasias, dysplasias, metaplasias, and hypertrophies. The neoplasms may be benign or malignant, and they may originate from any cell type, including but not limited to epithelial cells of various origin, muscle cells, and endothelial cells.

The present invention also provides methods of hormone replacement therapy in post-menopausal women, or in subjects after castration, comprising administering a nanoparticulate megestrol composition of the invention. Further, the compositions of the present invention may be used for ovarian suppression in several situations such as endometriosis, hirsutism, dysmenorrhea, and uterine bleeding.

The present invention also provides methods of oral contraception comprising administering a nanoparticulate megestrol composition of the invention. In one embodiment, the compositions of the invention are administered in combination with estrogen or a synthetic estrogen.

2. Dosage Forms of the Invention

The nanoparticulate megestrol compositions of the invention can be administered to a subject via any conventional means including, but not limited to, orally, rectally, ocularly, parenterally (e.g., intravenous, intramuscular, or subcutaneous), intracisternally, pulmonary, intravaginally, intraperitoneally, locally (e.g., powders, ointments or drops), or as a buccal or nasal spray. As used herein, the term "subject" is used to mean an animal, preferably a mammal, including a human or non-human. The terms patient and subject may be used interchangeably.

Moreover, the nanoparticulate megestrol compositions of the invention can be formulated into any suitable dosage form, including but not limited to liquid dispersions, gels, aerosols, ointments, creams, controlled release formulations, fast melt formulations, lyophilized formulations, tablets, capsules, delayed release formulations, extended release formulations, pulsatile release formulations, and mixed immediate release and controlled release formulations.

Nanoparticulate megestrol compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles including water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

The nanoparticulate megestrol compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the growth of microorganisms can be ensured by various antibacterial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, such as aluminum monostearate and gelatin.

Solid dosage forms for oral administration include, but are not limited to, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active agent is admixed with at least one of the following: (a) one or more inert excipients (or carriers), such as sodium citrate or dicalcium phosphate; (b) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (c) binders, such as carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (d) humectants, such as glycerol; (e) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (f) solution retarders, such as paraffin; (g) absorption accelerators, such as quaternary ammonium compounds; (h) wetting agents, such as cetyl alcohol and glycerol monostearate; (i) adsorbents, such as kaolin and bentonite; and (j) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. For capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Liquid nanoparticulate megestrol dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to megestrol, the liquid dosage forms may comprise inert diluents commonly used in the art, such as water or other solvents, solubilizing agents, and emulsifiers. Exemplary emulsifiers are ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, such as cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, fatty acid esters of sorbitan, or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

3. Dosage Quantities for the Nanoparticulate Megestrol Compositions of the Invention

The present invention provides a method of achieving therapeutically effective plasma levels of megestrol in a subject at a lower dose than the standard commercial formulations. This can permit smaller dosing volumes depending on the megestrol concentration chosen. Such a method comprises orally administering to a subject an effective amount of a nanoparticulate megestrol composition.

The nanoparticulate megestrol composition, when tested in fasting subjects in accordance with standard pharmacokinetic practice, produces a maximum blood plasma concentration profile of megestrol of greater than about 30 ng/ml in less than about 5 hours after the initial dose of the composition.

As used herein, the phrase "maximum plasma concentration" is interpreted as the maximum plasma concentration that megestrol will reach in fasting subjects.

A suitable dose of megestrol, administered according to the method of the invention, is typically in the range of about 1 mg/day to about 1000 mg/day, or from about 40 mg/day to about 800 mg/day. Preferably, the therapeutically effective amount of the megestrol of this invention is about ⅙, about ⅕, about ¼, about ⅓rd, or about ½ of the therapeutically effective amount of existing commercial megestrol formulations, e.g., Megace®g. "Therapeutically effective amount" as used herein with respect to a drug dosage, shall mean that dosage that provides the specific pharmacological response for which the drug is administered in a significant number of subjects in need of such treatment. It is emphasized that "therapeutically effective amount," administered to a particular subject in a particular instance will not always be effective in treating the diseases described herein, even though such dosage is deemed a "therapeutically effective amount" by those skilled in the art. It is to be further understood that drug dosages are, in particular instances, measured as oral dosages, or with reference to drug levels as measured in blood.

One of ordinary skill will appreciate that effective amounts of megestrol can be determined empirically and can be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester, or prodrug form. Actual dosage levels of megestrol in the nanoparticulate compositions of the invention may be varied to obtain an amount of megestrol that is effective to obtain a desired therapeutic response for a particular composition and method of administration. The selected dosage level therefore depends upon the desired therapeutic effect, the route of administration, the potency of the administered megestrol, the desired duration of treatment, and other factors.

Dosage unit compositions may contain such amounts of such submultiples thereof as may be used to make up the daily dose. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors: the type and degree of the cellular or physiological response to be achieved; activity of the specific agent or composition employed; the specific agents or composition employed; the age, body weight, general health, sex, and diet of the patient; the time of administration, route of administration, and rate of excretion of the agent; the duration of the treatment; drugs used in combination or coincidental with the specific agent; and like factors well known in the medical arts.

The following examples are given to illustrate the present invention. It should be understood, however, that the invention is not to be limited to the specific conditions or details described in these examples. Throughout the specification, any and all references to a publicly available document, including a U.S. patent, are specifically incorporated by reference.

In the examples that follow, the value for D50 is the particle size below which 50% of the megestrol particles fall. Similarly, D90 is the particle size below which 90% of the megestrol particles fall.

The formulations in the examples that follow were also investigated using a light microscope. Here, "stable" nanoparticulate dispersions (uniform Brownian motion) were readily distinguishable from "aggregated" dispersions (relatively large, nonuniform particles without motion). Stable, as known in the art and used herein, means the particles don't substantially aggregate or ripen (increase in fundamental particle size).

EXAMPLE 1

The purpose of this example was to describe preparation of nanoparticulate dispersions of megestrol acetate.

Formulations 1, 2, 3, 4 and 5, shown in Table 1, were milled under high energy Milling conditions using a NanoMill® (Elan Drug Delivery, Inc.) (see e.g., WO 00/72973 for "Small-Scale Mill and Method Thereof") and a Dyno®-Mill (Willy Bachofen AG).

TABLE 1

Formulation	Quantity of Megestrol	Identity and Quantity of Primary Surface Stabilizer	Identity and Quantity of Secondary Surface Stabilizer	Mean (nm)	D90 (nm)
1	5%	1% HPC-SL	0.05% DOSS	167	224
2	5%	1% HPMC	0.05% DOSS	156	215
3	5%	1% PVP	0.05% DOSS	167	226
4	5%	1% Plasdone ® S630*	0.05% DOSS	164	222
5	5%	1% HPMC	0.05% SLS	148	208

*Plasdone ® S630 (ISP) is a random copolymer of vinyl acetate and vinyl pyrrolidone.

Formulations 1–5 showed small, well-dispersed particles using the Horiba La-910 Laser Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, Calif.) and light microscopy. Formulations 1–5 were stable in electrolyte fluids and had acceptable physical stability at 5° C. for 4 weeks. Electrolyte fluids are representative of physiological conditions found in the human body. Formulations 1, 2, 3, and 4 also exhibited acceptable stability at 25° C. and 40° C. for 4 weeks. Formulation 5 exhibited acceptable stability at 40° C. for at least 3 weeks.

EXAMPLE 2

This example compares the pharmacokinetic parameters of nanoparticulate megestrol acetate formulations of the present invention with conventional microparticulate formulations of megestrol acetate.

Twelve male beagles, at least twelve months of age, were divided into 2 groups based on whether they were fasting or being fed. The dogs were acclimated for thirteen days prior to dosing. The animals weighed approximately 11.4 to 14.3 kg at the time of dosing, and the dose was adjusted to 10

mg/kg. Water was available ad libitum. The animals were fasted (food only) for twelve to sixteen hours prior to dosing on day 1. On day 1, each dog was administered a formulation by gavage. Following dosing, the gavage tube was flushed with 18 ml of water. In the fed study, the animals were fed a high fat meal about 1 hour prior to dosing.

The dogs were subdivided into four groups, with each group receiving either Formulation A (nanoparticulate megestrol dispersion #1, comprising 4.0% megestrol acetate, 0.8% HPMC, and 0.4% DOSS), Formulation B (nanoparticulate megestrol dispersion #2, comprising 4.0% megestrol acetate, 0.8% HPMC, and 0.04% SLS), Formulation C (suspension of microparticulate megestrol acetate, Par Pharmaceutical, Inc., New York) or Formulation D (Megace® Oral Suspension, which is a suspension of microparticulate megestrol acetate). Each formulation was adjusted to administer a dose of 10 mg/kg of megestrol acetate to the subject.

Prior to dosing, blood samples were taken from each subject. Blood samples were then collected from each subject at 15 and 30 minutes, as well as 1, 2, 3, 4, 6, 8, 24, 48, and 72 hours after dosing and centrifuged. Plasma was then separated and diluted when necessary, and subsequently analyzed for megestrol acetate by HPLC.

Tables 2 and 3 summarize the pharmacokinetic data of the four formulations administered to fasted dogs and fed dogs, respectively.

TABLE 2

Summary of Pharmacokinetic Data in Fasted Dogs

Parameters	Formulation A n = 3 (Mean ± SD)	Formulation B n = 3 (Mean ± SD)	Formulation C n = 3 (Mean ± SD)	Formulation D n = 3 (Mean ± SD)
AUC_{0-t}	37774.23 ± 11648.60	21857.68 ± 10737.53	17395.95 ± 10428.73	10094.30 ± 1990.89
AUC_{0-inf}	49408.88 ± 3392.80	27863.56 ± 15279.16	6948.48±*	12007.13 ± 1923.80
C_{max}	2209.74 ± 351.54	1563.02 ± 787.37	484.98 ± 321.70	339.92 ± 175.86
T_{max}	0.83 ± 0.29	0.50 ± 0.00	18.67 ± 9.24	2.67 ± 0.58
$t_{1/2}$	42.01 ± 33.81	30.09 ± 19.37	26.57±*	25.59 ± 7.11
K_{el}	0.025 ± 0.018	0.032 ± 0.024	0.026±*	0.028 ± 0.007

AUC_{0-t} (ng · hr/ml) = Area under the curve from time zero to the last measurable concentration;

AUC_{0-inf} (ng · hr/ml) = Area under the curve from time zero to infinity;

C_{max} (ng/ml) = Maximum plasma concentration;

T_{max} (hr) = Time to occurrence of C_{max};

$t_{1/2}$ (hr) = Apparent elimination half-life;

K_{el} (1/hr) = elimination rate constant;

*n = 1.

TABLE 3

Summary of Pharmacokinetic Data in Fed Dogs

Parameters	Formulation A n = 3 (Mean ± SD)	Formulation B n = 3 (Mean ± SD)	Formulation C n = 3 (Mean ± SD)	Formulation D n = 3 (Mean ± SD)
AUC_{0-t}	48543.56 ± 11608.55	36687.92 ± 12016.26	27332.11 ± 6488.79	31397.16 ± 5823.79
AUC_{0-inf}	61734.90 ± 4918.52	42787.74 ± 14630.92	31720.98 ± 5580.32	40218.66 ± 8649.33*
C_{max}	3777.34 ± 2489.41	2875.82 ± 1334.32	2180.73 ± 406.28	2577.83 ± 665.31
T_{max}	1.67 ± 2.02	3.00 ± 4.33	1.00 ± 0.00	0.83 ± 0.29
$T_{1/2}$	34.35 ± 12.10	26.67 ± 7.80	26.16 ± 10.88	36.60 ± 9.62*
K_{el}	0.022 ± 0.009	0.028 ± 0.010	0.31 ± 0.16	0.20 ± 0.005

AUC_{0-t} (ng · hr/ml) = Area under the curve from time zero to the last measurable concentration;

AUC_{0-inf} (ng · hr/ml) = Area under the curve from time zero to infinity;

C_{max} (ng/ml) = Maximum plasma concentration;

T_{max} (hr) = Time to occurrence of C_{max};

$T_{1/2}$ (hr) = Apparent elimination half-life;

K_{el} (1/hr) = elimination rate constant;

*n = 2.

The results in the fasted dogs show that the nanoparticulate megestrol formulations (Formulations A and B) showed dramatically superior bioavailability, as evidenced by the superior AUC and C_{max} results, as compared to the conventional microparticulate megestrol formulations (Formulations C and D). Formulation A, with a C_{max} of 2210, had a maximum concentration more than 4½ times that of Formulation C (485), and a maximum concentration more than 6½ times that of Formulation D (340). Formulation B, with a C_{max} of 1563, had a maximum concentration more than 3.2 times that of Formulation C (485), and a maximum concentration more than 4.6 times that of Formulation D (340). Also, Formulation A, with an AUC of 49,409 ng hr/mL, had an oral bioavailability more than 7 times that of Formulation C (6948 ng hr/mL) and an oral bioavailability of more than 4 times that of Formulation D (12007 ng hr/mL). Formulation B, with an AUC of 27,864 ng hr/mL, had an oral bioavailability more than 4 times that of Formulation C (6949 ng hr/mL) and an oral bioavailability more than 2 times that of Formulation D (12,007 ng hr/mL).

In addition, in the fasted dogs the nanoparticulate megestrol formulations (Formulations A and B) showed dramatically superior faster onset of action, as evidenced by the superior T_{max} results, as compared to the conventional microparticulate megestrol formulations (Formulations C and D). Formulation A, with a T_{max} of 0.83 hr, reached a maximum concentration of megestrol in less than $1/20^{th}$ the time of Formulation C (18.67 hr), and in less than $1/3^{rd}$ the time of Formulation D (2.67 hr). Formulation B, with a T_{max} of 0.50 hr, reached a maximum concentration in less than $1/37^{th}$ the time of Formulation C (18.67 hr), and in less than $1/5^{th}$ the time of Formulation D (2.67 hr).

Similarly, the results in the fed dogs show that the nanoparticulate megestrol formulations (Formulations A and B) showed dramatically superior bioavailability, as evidenced by the superior AUC and C_{max} results, as compared to the conventional microparticulate megestrol formulations (Formulations C and D). Formulation A, with a C_{max} of 3777, had a maximum concentration of about more than 1.7 times that of Formulation C (2181), and a maximum concentration of about more than 1.5 times that of Formulation D (2578). Formulation B, with a C_{max} of 2876, had a maximum concentration of about more than 1.3 times that of Formulation C (2181), and a maximum concentration of about more than 1.1 times that of Formulation D (2578). Formulation A, with an AUC of 61,735 ng hr/mL, had an oral bioavailability of more than 1.9 times that of Formulation C (31721 ng hr/mL) and more than 1.5 times that of Formulation D (40219 ng hr/mL). Formulation B, with an AUC of 42788 ng hr/mL, had an oral bioavailability of more than 1.3 times that of Formulation C (31721 ng hr/mL) and an oral bioavailability of more than 1.1 times that of Formulation D (40218 ng hr/mL).

EXAMPLE 3

This example demonstrates the physical stability of megestrol acetate dispersions at various concentrations and with the addition of sucrose, flavoring, and preservatives. Megestrol acetate was milled under high energy milling conditions using a NanoMill™2 System (Elan Drug Delivery, Inc.) in the presence of a preservative/buffer system consisting of sodium benzoate, citric acid monohydrate, and sodium citrate dihydrate. After milling, the resulting dispersion was diluted with water, sucrose, flavoring, and additional preservative/buffer to prepare dispersions containing 3% (w/w), 5% (w/w), or 9% (w/w) megestrol acetate. The resulting formulations are shown in Table 4. The physical stability of the formulations was then monitored at 25° C., 40° C., and 50° C.

TABLE 4

	Formulation Summary			
	Concentrated	Diluted, Flavored Dispersions		
API and Excipients	Nanoparticle Dispersion g/kg	Formulation E 3% Dispersion g/kg	Formulation F 5% Dispersion g/kg	Formulation G 9% Dispersion g/kg
Megestrol Acetate, USP	325.000	30.000	50.000	90.000
Hydroxypropyl Methylcellulose, USP	65.000	6.000	10.000	18.000
Docusate Sodium, USP	3.250	0.300	0.500	0.900
Sodium Benzoate, USP	1.214	1.826	1.777	1.681
Sodium Citrate Dihydrate, USP	0.910	0.091	0.089	0.084
Citric Acid Monohydrate, USP	0.061	1.369	1.333	1.260
Sucrose, USP		50.000	50.000	50.000
Natural and Artificial Lemon Flavor		0.400	0.400	0.400
Artificial Lime Flavor		0.400	0.400	0.400
Purified Water, USP	604.600	909.614	885.500	837.280

Particle size measurements (Table 5) were used to assess the physical stability. The results show almost no increase in the mean particle size at either 25° C. or 40° C., and only a slight increase in the mean particle size at 50° C. 126 days of stability measurements were obtained for the 5% and 9% dispersions and 33 days of stability were obtained for the 3% dispersion, which was prepared at a later date.

TABLE 5

	Mean particle size (nm)								
	3% Dispersion			5% Dispersion			9% Dispersion		
	25° C.	40° C.	50° C.	25° C.	40° C.	50° C.	25° C.	40° C.	50° C.
0 days	148	148	148	169	169	169	169	169	169
30 days				172	171	187	172	170	179
33 days	141	144	173						
126 days				171	174	188	168	175	182

EXAMPLE 4

The purpose of this Example was to demonstrate the improved viscosity characteristics of the dispersions of this invention.

The viscosities of three formulations of this invention (E, F, and G as described in Example 3) and two conventional commercial formulations (Formulations C and D as described in Example 2) were determined using a rheometer (model CVO-50, Bohlin Instruments). The measurements were performed at a temperature of 20° C. using a double gap (40/50) geometry.

The viscosities of the Formulations of this invention were found to be nearly Newtonian (i.e., the viscosity being independent of shear rate), and were 1.5, 2.0, and 3.5 mPa s for the 30, 50, and 90 mg/mL concentrations, respectively.

The viscosity dependence on concentration is illustrated in FIG. **1**.

The commercial formulations C and D were shear thinning in nature. Such samples cannot be characterized by a single viscosity but rather a series of viscosities measured at different shear rates. This is most conveniently illustrated as viscosity—shear rate curves as shown in FIG. **2**.

The commercial samples and the three formulations of this invention are compared in Table 6 below. Viscosities are in units of mPa s.

TABLE 6

Shear Rates of Commercial Megestrol Formulations (D and C) and the Nanoparticulate Megestrol Formulations of the Invention (E, F, & G)

	Commercial Samples		Formulations E, F, & G		
Shear Rate s^{-1}	Formulation D (mPa s)	Formulation C (mPa s)	(E) 30 mg/mL (mPa s)	(F) 50 mg/mL (mPa s)	(G) 90 mg/mL (mPa s)
0.1	4010	2860	1.5	2.0	3.5
1	929	723	"	"	"
10	215	183	"	"	"
100	49.9	46.3	"	"	"

* These samples were not measured at the 0.1 and 1 s^{-1} shear rates (the shear range was ca 2 to 100 s^{-1}) but the assessment that these exhibit Newtonian flow properties justifies the entries.

EXAMPLE 5

The purpose of this Example was to visually demonstrate the difference between the viscosity characteristics of liquid megestrol formulations of the invention as compared to conventional liquid megestrol formulations.

A sample of a 50 mg/mL nanoparticulate dispersion of megestrol acetate and two conventional commercial formulations at 40 mg/mL (Formulations C and D as described in Example 2) were each placed in a vial, which was then shaken. Attached as FIG. **3** is a photograph of the thee vials, which from left to right are the nanoparticulate megestrol acetate dispersion, Formulation C, and Formulation D.

The vial with the nanoparticulate dispersion shows a thin, silky, almost shear film coating the vial. In contrast, the vials containing the two commercial formulations show a gritty residue coating. Such a gritty residue is the same residue which coats a patient's mouth and throat upon administration. Such a coating is highly unpleasant, particularly for patients suffering from wasting (i.e., unable to eat). Thus, FIG. **3** visually demonstrates the appeal of a liquid oral nanoparticulate megestrol formulation of the invention as compared to conventional commercial liquid oral megestrol formulations.

EXAMPLE 6

The purpose of this example was to prepare nanoparticulate compositions of megestrol acetate using various surface stabilizers.

5% megestrol acetate (Par Pharmaceuticals, Inc.) was combined with 1.25% of various surface stabilizers: tyloxapol (Sterling Organics), Tween 80 (Spectrum Quality Prod-

ucts), Pluronic F-108 (BASF), Plasdone S-630 (ISP), hydroxypropylmethylcellulose (HPMC) (Shin Etsu), hydroxypropylcellulose (HPC-SL) (Nippon Soda Co., Ltd.), Kollidon K29/32 (polyvinylpyrrolidone) (ISP), or lysozyme (Fordras).

For each combination of megestrol acetate and surface stabilizer, the surface stabilizer was first dissolved in 7.875 g water for injection (WFI) (Abbott Laboratories, Inc.), followed by the addition of the milling media, PolyMill™-500 (Dow Chemical, Co.), and 0.42 g megestrol.

The slurries were charged into each of eight 18 cc NanoMill® (Elan Drug Delivery) chambers and milled for 30 min. Upon completion of milling the dispersions were harvested with a 26 gauge needle yielding the following particle sizes shown in Table 7.

All particle size distribution analyses were conducted on a Horiba LA-910 Laser Light Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, Calif.). RO-water was utilized as the liquid dispersing medium and a flow-through sample cell was used for all measurements. All samples were assayed in 150 cc liquid medium.

TABLE 7

Megestrol Conc.	Surface Stabilizer/Conc.	Mean Particle Size
5%	tyloxapol; 1.25%	214 nm
5%	Tween 80; 1.25%	210 nm
5%	Pluronic F-108; 1.25%	459 nm
5%	Plasdone S-630; 1.25%	292 nm
5%	HPMC; 1.25%	314 nm
5%	HPC-SL; 1.25%	623 nm
5%	PVP K29/32; 1.25%	24816 nm
5%	lysozyme; 1.25%	179 nm

The results show that tyloxapol, Tween 80, and lysozyme produced small particles without substantial aggregation. Pluronic F-108, Plasdone S-630, HPMC, HPC-SL, and K29/32 had larger particle sizes, indicating that aggregation was occurring. Thus, at the particular concentration of drug and surface stabilizer, using the described milling method, Pluronic F-108, Plasdone S-630, HPMC, HPC-SL, and K29/32 were not preferable surface stabilizers. These surface stabilizers may be useful in nanoparticulate compositions of megestrol at different drug or surface stabilizer concentrations, or when used in conjunction with another surface stabilizer.

EXAMPLE 7

The purpose of this example was to prepare nanoparticulate compositions of megestrol acetate using various surface stabilizers.

Megestrol acetate (Par Pharmaceuticals, Inc.) and various surface stabilizers, as shown in Table 8, were combined and milled, followed by determination of the particle size and stability of the resulting composition. Materials were obtained as in Example 6.

All of the samples were milled using a Dyno®-Mill (Model KDL-Series, Willy Bachofen AG, Basel, Switzerland) equipped with a 150 cc stainless steel batch chamber. Cooling water (approximate temperature 5° C.) was circulated through the mill and chamber during operation.

All particle size distribution analyses were conducted on a Horiba LA-910 Laser Light Scattering Particle Size Distribution Analyzer (Horiba Instruments, Irvine, Calif.), as described above in Example 6.

Qualitative microscopic assessments of the formulations were performed using a Leica light microscope (Type 301-371.010). Sample preparation involved diluting the product dispersions in RO-water and dispensing about 10 μL onto a glass slide. Oil immersion was utilized in conjunction with 1000× magnification.

The physical stability was assessed by storing the dispersion is 20 ml glass scintillation vials in a temperature/humidity controlled chamber at either 5° C., (25° C./60% RH), (40° C./75% RH), (50° C./75% RH), or 55° C. Samples were taken at varying time intervals and the particle size was analyzed.

For all formulations, the surface stabilizer(s) was first dissolved in WFI (Abbott Laboratories, Inc.) (75.0 g for Exp. Nos. 1, 2, 3, 7, and 8; 75.2 g for Exp. Nos. 4 and 9; 74.9 g for Exp. Nos. 5 and 6; 70.3 g for Exp. Nos. 10 and 11), followed by combining the surface stabilizer solution megestrol acetate and PolyMill™-500 polymeric grinding media. This mixture was then added to the appropriate milling chamber, milled for the time period shown in Table 8, followed by harvesting and vacuum filtering of the megestrol acetate dispersion.

TABLE 8

Exp. No.	Megestrol Conc.	Surface Stabilizer(s) and Conc.	Milling Time	Mean Particle Size	Stability
1	5%	1.25% lysozyme	20 min.	209 nm	The sample showed substantial aggregation after incubation in normal saline for 30 minutes as determined by optical microscopy.
2	5%	1.25% Tween 80	75 min.	157 nm	Upon storage at 5° C. for 15 days the sample grew to a mean diameter of 577 nm.
3	5%	1.25% tyloxapol	2 hrs.	208 nm	Optical microscopoy revealed the presence of elongated "needle-like" crystals.
4	5%	1% Pluronic F127	2 hrs.	228 nm	Upon storage at 25° C. for 5 days the sample grew to a mean diameter of 308 nm.
5	5%	1.25% HPMC 0.0625% SLS[1]	75 min.	161 nm	Upon storage at 40° C. for 19 days, the sample grew to a mean diameter of 171 nm. Incubation for 30 minutes at 40° C. in 0.01 N HCl or normal saline resulted in particle sizes of 164 nm and 209 nm, respectively.
6	5%	1.25% HPC-SL, 0.05% SLS	60 min.	167 nm	Upon storage at 40° C. for 15 days, the sample grew to a mean diameter of 194 nm. Incubation for 30 minutes at 40° C. in 0.01 N HCl or normal saline resulted in particle sizes of 183 nm and 179 nm, respectively.
7	5%	1.25% HPMC	45 min.	185 nm	Upon storage at 40° C. for 6 days, the sample grew to a mean diameter of 313 nm. Incubation for 30 minutes at 40° C in 0.01 N HCl or normal saline

TABLE 8-continued

Exp. No.	Megestrol Conc.	Surface Stabilizer(s) and Conc.	Milling Time	Mean Particle Size	Stability
					resulted in particle sizes of 2041 nm and 1826 nm, respectively. Optical microscopy revealed aggregation in both the saline and HCl samples.
8	5%	1.25% HPC-SL	45 min.	176 nm	Upon storage at 40° C. for 6 days, the sample grew to a mean diameter of 244 nm. Incubation for 30 minutes at 40° C. in 0.01 N HCl or normal saline resulted in particle sizes of 873 nm and 524 nm, respectively. Optical microscopy revealed aggregation in both the saline and HCl samples.
9	5%	1% HPMC 0.05% SLS	70 min.	152 nm	Incubation for 30 minutes at 40° C. in 0.01 N HCl or normal saline resulted in particle sizes of 155 nm and 539 nm, respectively. Optical microscopy confirmed that aggregation was present in the sample incubated in saline.
10	10%	2% HPMC 0.1% DOSS[2]	70 min.	150 nm	Following harvesting the sample was diluted to 4% API by adding WFI. Upon storage at 40° C. for 40 days, the sample had a mean diameter of 146 nm. Optical microscopy revealed small, well dispersed particles.
11	10%	2% HPMC 0.1% SLS	70 min.	146 nm	Upon storage at 40° C. for 19 days, the sample had a mean diameter of 149 nm. Optical microscopy revealed small, well dispersed particles.
12	10%	4% lysozyme	60 min.	108 nm	Upon storage at 40° C. for 9 days the sample had a mean diameter of 124 nm. Optical microscopy revealed small, well dispersed particles.

[1]Sodium lauryl sulfate (Spectrum Quality Products)
[2]Dioctyl Sodium Sulfosuccinate (Cytec)

The results shown in Table 8 indicate that the use of lysozyme (Exp. No. 1) as a surface stabilizer resulted in small well dispersed particles with a mean particle size of 209 nm, but the formulation showed aggregation when diluted into a normal saline solution. A megestrol acetate/tyloxapol sample was also stable at higher drug and stabilizer concentrations (Exp. No. 12).

Tween 80, tyloxapol, and Pluronic F127 (Exp. Nos. 2, 3, and 4) were effective primary surface stabilizers and produced well-dispersed particles without significant aggregation. Stability measurements, however, revealed rapid crystal growth for all three stabilizers. 5% megestrol acetate/1.25% Tween 80 grew from 157 nm to 577 nm after 15 days at 5° C. 5% megestrol acetate/1.25% tyloxapol showed needle-like crystals when observed under optical microscopy. 5% megestrol acetate/1.25% Pluronic F127 grew from 228 nm to 308 nm after 5 days at 25° C. Because of the rapid crystal growth observed, Tween 80, tyloxapol, and Pluronic F127 were deemed not suitable surface stabilizers at the described drug/surface stabilizer concentrations prepared under the conditions described above.

The HPC-SL formulation (Exp. No. 8) showed substantial aggregation indicating that a secondary charged stabilizer would be needed. SLS was added (Exp. No. 6) and the new formulation grew from 167 to 194 nm after storage at 40° C. for 15 days and did not show any substantial aggregation upon incubation in either 0.01N HCl or normal saline. The SLS appeared effective at preventing the aggregation but the sample showed some particle size growth.

The HPMC formulation (Exp. No. 7) showed substantial aggregation indicating that a secondary charged stabilizer would be needed. SLS was added (Exp. Nos. 5 and 11), and the new formulations showed only minimal growth from 161 nm to 171 nm (Exp. No. 5), and from 146 to 149 nm (Exp. No. 11), after storage at 40° C. for 19 days. In addition, the composition of Exp. No. 5 did not show any substantial aggregation upon incubation in either 0.01N HCl or normal saline. The SLS was effective at preventing the aggregation without causing significant crystal growth.

An attempt was made to reduce the concentration of the primary and secondary stabilizers (Exp. No. 9) and resulted in a post-milling mean diameter of 152 nm. Incubation for 30 minutes at 40° C. in normal saline resulted in particle sizes of 539 nm. Optical microscopy confirmed that aggregation was present in the sample incubated in saline.

Docusate sodium (DOSS) was tried as a secondary stabilizer (Exp. No. 10) and resulted in well-dispersed particles with a mean diameter of 150 nm. Upon storage at 40° C. for 40 days, the sample had a mean diameter of 146 nm. Optical microscopy revealed small, well-dispersed particles. DOSS seemed to result in even less particle size growth than SLS.

EXAMPLE 8

The purpose of this example was to prepare nanoparticulate compositions of megestrol acetate using various surface stabilizers and further including preservatives or excipients.

The materials and methods were the same as in Example 7, except that for several of the examples different sources of megestrol acetate were used (See Table 9). In addition, for Exp. Nos. 5, a NanoMill® milling system (Elan Drug Delivery) was used. Several different combinations of megestrol acetate, surface stabilizer(s), and one or more preservatives or excipients were prepared, following by testing the compositions for particle size and stability.

The surface stabilizer(s) and one or more preservatives were first dissolved in WFI, followed by combining the solution with megestrol acetate and the grinding media. This mixture was then added to the milling chamber and milled for the time period set forth in Table 9, below.

For several of the experiments, following milling the megestrol acetate dispersion was combined with a flavored suspension. The stability of the resultant composition was then evaluated.

The formulation details and results are shown in Table 9, below.

TABLE 9

Exp.	Megestrol Conc.	Surface Stabilizer(s) and Conc.	Preservatives/Excipients	Milling Time	Mean Particle Size	Stability
1	10%	2% HPMC 0.1% DOSS	Sodium Benzoate (0.4 g), Sodium Citrate Dihydrate (20 mg) Citric Acid Monohydrate (0.3 g)	75 min	146 nm	After milling a flavored suspension was prepared by adding sucrose (2.5 g), xanthan gum (0.113 g), glycerol (13.75 g), lemon flavor (0.1 g), WFI (18.6 g), and 20.0 g of the milled dispersion. Upon storage at 40° C. for 24 days, the sample showed aggregation with a mean diameter of 837 nm. Incubation for 30 minutes at 40° C. in 0.01 N HCl or normal saline resulted in particle sizes of 206 nm and 3425 nm, respectively. Optical microscopy confirmed that the sample incubated in saline had aggregated.
2	25%	5% HPMC 0.05% DOSS	Sodium Benzoate (0.11 g) Citric Acid Monohydrate (0.08 g)	95 min.	See right column.	16 g of the milled drug dispersion was combined with sucrose (5 g), lime flavor (80 mg), and WFI (78.9 g). The diluted drug dispersion had a mean diameter of 192. After 6 days at 55° C. the particles had a mean diameter of 10 microns, indicating substantial aggregation
3	25%	5% HPMC, 0.15% DOSS	Sodium Benzoate (0.11 g) Citric Acid Monohydrate (0.08 g)	95 min.	See right column.	16 g of the milled drug dispersion was combined with sucrose (5 g), lime flavor (80 mg), and WFI (78.9 g). The diluted drug dispersion had a mean diameter of 173 nm. After 12 days at 55° C. the particles had a mean diameter of 295 nm.
4	32.5%1	6.5% HPMC 0.33% DOSS	Sodium Benzoate (13.07 g) Sodium Citrate Dihydrate (0.65 g) Citric Acid Monohydrate (9.8 g)	15.5 hrs	160 nm	Upon storage at 50° C. for 44 days, the mean diameter was 190 nm.
5	32.5%	6.5% HPMC 0.33% DOSS	Sodium Benzoate (9.71 g) Sodium Citrate Dihydrate (0.49 g) Citric Acid Monohydrate (7.28 g)	12 hrs	147 nm	Upon storage at 50° C. for 44 days the mean diameter was 178 nm.

[1]Pharmacia
[2]Pharmabios

In Exp. No. 1 of Table 9, a sweetened, flavored dispersion was prepared by mimicking the current commercial formulation of megestrol acetate that contains sucrose, xanthan gum, glycerol, lemon and lime flavors, and is preserved and buffered with sodium benzoate and citric acid. Upon storage at 40° C. for 24 days the sample showed aggregation with a mean diameter of 837 nm. Incubation for 30 minutes at 40° C. in 0.01N HCl or normal saline resulted in particle sizes of 206 nm and 3425 nm, respectively. Optical microscopy confirmed that the sample incubated in saline had aggregated. The aggregation upon storage indicated that this particular combination of drug and surface stabilizer, at the concentrations used and methodology employed to make the compositions, would not be an effective formulation.

For Exp. Nos. 4 and 5, the formulation was scaled-up in a NanoMill™-2 system to determine if the scale-up would effect the physical stability. Two different sources of megestrol acetate were tested: Pharmacia and Pharmabios. The product of Exp. No. 4 had a mean diameter of 160 nm without ultrasound. Upon storage at 50° C. for 44 days the mean diameter was 190 nm. The composition of Exp. No. 5 had a post-milling mean diameter of 147 nm without ultrasound. Upon storage at 50° C. for 44 days the mean diameter was 178 nm. Both sources of active agent milled effectively and showed little particle size growth even at 50° C.

The results of Examples 6 and 7 showed that high energy milling with polymeric attrition media could be used to produce stable nanoparticulate colloidal dispersions of megestrol acetate suitable for oral administration to animals or humans. The primary stabilizer HPMC required the presence of DOSS or SLS to prevent aggregation at the concentrations of drug and stabilizer tested (other combinations of drug and HPMC concentrations may result in a stable composition without the addition of a second surface stabilizer). In general, average particle sizes of less than about 160 nm could be obtained. Tests conducted with two sources of megestrol acetate revealed that both sources milled effectively and exhibited excellent physical stability.

Based on mean particle size, physical stability, and the pre-clinical dog study, the best nanoparticulate megestrol acetate formulation for commercial development, based on the results of the data given in the examples, consisted of 32.5% megestrol acetate, 6.5% HPMC, and 0.325% DOSS (i.e., a drug:HPMC ratio of 1:5 and a drug:DOSS ratio of 1:100. The formulation milled effectively in the presence of preserved water (0.2% sodium benzoate, 0.01% sodium citrate dihydrate, and 0.15% citric acid monohydrate). Upon dilution with preserved water, flavors, and sucrose none of the dispersions showed severe aggregation, except for the dispersions containing xanthan gum (data not shown) or low levels of DOSS. The alcohol-based flavors did not effect the physical stability nor did several freeze-thaw cycles (data not shown).

EXAMPLE 9

This example compares the pharmacokinetic parameters of nanoparticulate megestrol acetate formulations of the invention with a conventional microparticulate formulation of megestrol acetate. Results were obtained from a fasted study group consisting of 36 male subjects, 18 years of age or older. For a fed study group, results from 32 subjects were analyzed.

Subjects in the fasted study group and the fed study group were administered study drugs in four successive periods. Treatment A (1×150 mg drug as 5 ml of a 3% megestrol acetate nanoparticulate formulation) was administered in the first period. Reference Treatment B (1×800 mg drug as 20

ml of a 4% megestrol acetate Megace® Oral Suspension) was administered in the second period. Treatment C (1×250 mg drug as 5 ml of a 5% megestrol acetate nanoparticulate formulation) was administered in the third period. Treatment D (1×450 mg drug as 5 ml of a 9% megestrol acetate nanoparticulate formulation) was administered in the fourth period. The formulations of Treatments A, C, and D are listed in Table 10 below, with particle size information (microns) provided in Table 11.

In each period, subjects were confined from at least 10 hours prior to drug administration to after the last sample collection. In the fasted study group, no food was consumed from at least 10 hours before dosing to at least 4 hours after dosing. In the fed study group, a high-calorie breakfast (containing about 800 to 1000 calories, approximately 50% of which were from fat) was served within 30 minutes prior to dosing; dosing occurred within 5 minutes after the breakfast was completed. A controlled meal was served to both groups after 4 hours after dosing, and standard meals were served at appropriate times thereafter. The meals in all four periods were identical. Subjects in the fasted study group were not allowed fluid intake from 1 hour before dosing to 1 hour after. Subjects in the fed study group were also not allowed fluid intake during this period except for fluids provided with the high-calorie breakfast. Water was provided ad libitum to both study groups at all other times.

Blood samples were obtained before dosing, at half-hourly intervals in the 6 hours following dosing, and at 7, 8, 12, 16, 20, 24, 36, 48, 72, and 96 hours after dosing. Megestrol acetate in plasma samples was then determined.

Table 12 below summarizes pharmacokinetic data for the fasted study group, and Table 13 below summarizes pharmacokinetic data for the fed study group.

Treatments A, C, and D in fasting subjects produced dose-normalized values for AUC_{0-t} and AUC_{0-inf} that were approximately twice those of Reference Treatment B. Maximum dose-normalized megestrol acetate concentrations in Treatments A, C, and D were approximately 9 to 12 times that of Reference Treatment B. The maximum megestrol acetate concentration for the 150 mg-dose of Treatment A was approximately twice that of the 800 mg-dose of reference Treatment B. Moreover, comparable values of AUC_{0-t} and AUC_{0-inf} were observed for the 450 mg-dose of Treatment D and the 800 mg-dose of Reference Treatment B.

Treatments A, C, and D in fed subjects produced dose-normalized values for AUC_{0-t} and AUC_{0-inf} that were approximately 8 to 10% greater than those of Reference Treatment B. Maximum dose-normalized megestrol acetate concentrations in Treatments A, C, and D were approximately 38 to 46% greater than that of Reference Treatment B. Megestrol acetate onset for Treatments A, C, and D was comparable to Reference Treatment B.

Nanoparticulate megestrol acetate formulations, therefore, exhibited superior oral bioavailability, relative to the Megace® Oral Suspension, in fasting and fed human subjects.

TABLE 10

Formulations for Megestrol Acetate Oral Suspension 3, 5% and 9%

	Strengths		
Ingredients	3% w/w (30 mg/mL)	5% w/w (50 mg/mL)	9% w/w (90 mg/mL)
Megestrol Acetate	3.000	5.000	9.000
Hydroxypropyl Methylcellulose	0.600	1.000	1.800
Docusate Sodium	0.030	0.050	0.090
Sodium Benzoate	0.183	0.178	0.168
Sodium Citrate Dihydrate	0.009	0.009	0.008
Citric Acid Monohydrate	0.137	0.133	0.126
Sucrose	5.000	5.000	5.000
Natural and Artificial Lemon Flavor	0.040	0.040	0.040
Artificial Lime Flavor	0.040	0.040	0.040
Purified Water	90.961	88.550	83.727
TOTAL	100.000	100.000	100.000

TABLE 11

Particle Size Data for the Megestrol Acetate Oral Suspensions*

	Strength 30 mg/g			Strength 50 mg/g			Strength 90 mg/g		
	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)
Initial	0.068	0.123	0.223	0.069	0.125	0.229	0.068	0.124	0.227
ACC/1 month	0.070	0.129	0.237	0.070	0.127	0.231	0.070	0.127	0.230
ACC/2 months	0.070	0.127	0.231	0.070	0.127	0.233	0.073	0.126	0.221
ACC/3 months	0.070	0.129	0.237	0.070	0.128	0.235	0.070	0.128	0.234

TABLE 11-continued

Particle Size Data for the Megestrol Acetate Oral Suspensions*

	Strength 30 mg/g			Strength 50 mg/g			Strength 90 mg/g		
	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)	d(0.1)	d(0.5)	d(0.9)
Initial	0.068	0.123	0.223	0.069	0.125	0.229	0.068	0.124	0.227
RT 3 months	0.070	0.128	0.237	0.073	0.128	0.224	0.067	0.121	0.223

*All particle sizes are given in microns. "d(0.1)" means distribution of smallest 10% of the particles, i.e., d(0.1) 10 μm means 10% of the particles are less than 10%. Similarly, "d(0.5)" means distribution of the smallest 50% of the particles, and "d(0.9)" means distribution of the smallest 90% of the particles. Thus, d(0.9) means that 90% of the particles are less than XX μm.

TABLE 12

Summary of Pharmacokinetic Data in Fasted Human Subjects*

Parameters	Treatment A (Mean ± SD)	Ref. Treatment B (Mean ± SD)	Treatment C (Mean ± SD)	Treatment D (Mean ± SD)
AUC_{0-t}	2800 ± 900	7000 ± 5000	4700 ± 1800	8500 ± 3200
AUC_{0-inf}	3100 ± 1000	9000 ± 9000	5200 ± 2100	9000 ± 4000
C_{max}	410 ± 120	190 ± 110	650 ± 200	950 ± 270
T_{max}	1.7 ± 0.9	6 ± 6	1.6 ± 1.0	1.7 ± 1.1
$t_{1/2}$	35 ± 13	31 ± 19	34 ± 10	34 ± 12
K_{el}	0.023 ± 0.011	0.026 ± 0.009	0.022 ± 0.008	0.023 ± 0.008

AUC_{0-t} (ng · hr/ml) = Area under the curve from time zero to the last measurable concentration;
AUC_{0-inf} (ng · hr/ml) = Area under the curve from time zero to infinity;
C_{max} (ng/ml) = Maximum plasma concentration;
T_{max} (hr) = Time to occurrence of C_{max};
$t_{1/2}$ (hr) = Apparent elimination half-life;
K_{el} (1/hr) = Elimination rate constant;
*n = 36.

TABLE 13

Summary of Pharmacokinetic Data in Fed Human Subjects*

Parameters	Treatment A (Mean ± SD)	Ref. Treatment B (Mean ± SD)	Treatment C (Mean ± SD)	Treatment D (Mean ± SD)
AUC_{0-t}	3500 ± 1100	17000 ± 5000	5700 ± 1600	10500 ± 3000
AUC_{0-inf}	3900 ± 1300	19000 ± 6000	6300 ± 2000	12000 ± 4000
C_{max}	380 ± 140	1400 ± 400	590 ± 170	1080 ± 290
T_{max}	3.8 ± 3.5	3.9 ± 0.9	3.4 ± 1.7	3.2 ± 1.7
$t_{1/2}$	35 ± 12	33 ± 9	35 ± 10	38 ± 12
K_{el}	0.023 ± 0.013	0.023 ± 0.007	0.023 ± 0.009	0.021 ± 0.008

AUC_{0-t} (ng · hr/ml) = Area under the curve from time zero to the last measurable concentration;
AUC_{0-inf} (ng · hr/ml) = Area under the curve from time zero to infinity;
C_{max} (ng/ml) = Maximum plasma concentration;
T_{max} (hr) = Time to occurrence of C_{max};
$t_{1/2}$ (hr) = Apparent elimination half-life;
K_{el} (1/hr) = Elimination rate constant;
*n = 32.

It will be apparent to those skilled in the art that various modifications and variations can be made in the methods and compositions of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

We claim:

1. A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:

(a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;

(b) the megestrol acetate formulation comprises megestrol particles having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer associated with the surface of the megestrol particles; and

(c) the administration is once daily;

wherein after a single administration in a human subject of the formulation there is no substantial differ-

ence in the C_{max} of megestrol when the formulation is administered to the subject in a fed versus a fasted state,

wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing.

2. The method of claim **1**, wherein the anorexia, cachexia or loss of body mass is associated with a diagnosis of HIV or AIDS in the human patient.

3. The method of claim **1**, wherein the anorexia, cachexia or loss of body mass is associated with a diagnosis of cancer in the human patient.

4. A method of increasing the body mass in a human patient suffering from anorexia, cachexia, or loss of body mass, comprising administering to the human patient a megestrol formulation, wherein:

(a) the megestrol acetate formulation is a dose of about 40 mg to about 800 mg in about a 5 mL dose of an oral suspension;

(b) the megestrol acetate formulation comprises megestrol particles having an effective average particle size of less than about 2000 nm, and at least one surface stabilizer associated with the surface of the megestrol particles; and

(c) the administration is once daily;

wherein after a single administration in a human subject of the formulation the difference in the C_{max} of the megestrol when administered in a fed versus a fasted state is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%, wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing.

5. The method of claim **4**, wherein the difference in C_{max} is less than about 60%.

6. The method of claim **1**, wherein there is a difference in the mean T_{max} for the nanoparticulate megestrol composition when administered in fed versus fasted states, and that difference is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

7. The method of claim **1**, wherein formulation exhibits a mean C_{max} selected from the group consisting of greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130% greater than about 140%, and greater than about 150%, than the mean C_{max} exhibited by a standard commercial, non-nanoparticulate composition of megestrol, administered at the same dosage.

8. The method of claim **1**, wherein there is a difference in absorption (AUC) when the composition is administered in fed versus fasted states, and the difference is selected from the group consisting of less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

9. The method of claim **1**, wherein the anorexia, cachexia or loss of body mass is associated with cancer.

10. The method of claim **1**, wherein the anorexia, cachexia or loss of body mass is associated with HIV or AIDS.

11. The method of claim **1**, wherein a maximum blood plasma concentration of megestrol is attained in about 1 hour or less after administration of the megestrol formulation in fasting subjects.

12. The method of claim **1**, wherein a maximum blood plasma concentration of megestrol of at least about 700 ng/ml is obtained.

13. The method of claim **12**, wherein the maximum blood plasma concentration of megestrol is at least about 700 ng/ml and is attained in less than 5 hours after administration of the megestrol formulation.

14. The method of claim **1**, wherein the maximum blood plasma concentration of megestrol is at least about 400 ng/ml and is attained in less than 5 hours after administration of the megestrol formulation.

15. The method of claim **1**, wherein a mean C_{max} of about 300 ng/ml to about 2000 ng/ml is obtained after a single administration of the formulation in the human subject in a fasted state.

16. The method of claim **1**, wherein the surface stabilizer is selected from the group consisting of nonionic, cationic, ionic, and zwitterionic surfactants.

17. The method of claim **1**, wherein the surface stabilizer is selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin, dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, Tetronic 1508, (tetrafunctional block copolymer derived from the addition of propylene oxide and ethylene oxide to ethylenediamine having an average molecular weight of 30,000) alkyl aryl polyether sulfonate, mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), $C_{18}H_{37}CH_2(CON(CH_3)—CH_2(CHOH)_4(CH_2OH)_2$, decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, poly-n-methylpyridinium, anthryul pyridinium chloride, chitosan, polyl-

ysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide, hexyldesyltrimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, stearyltrimethylammonium chloride, benzyldi(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15} dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18})dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylaluminum bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts, alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, vinyl pyridine, lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, alkylimidazolium salt, imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, and cationic guar.

18. The method of claim **4**, wherein there is a difference in the mean T_{max} for the nanoparticulate megestrol composition when administered in fed versus fasted states, and that difference is selected from the group consisting of less than about 100%, less than about 90%, less than about 80%, less than about 70%, less than about 60%, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

19. The method of claim **4**, wherein the formulation exhibits a mean C_{max} selected from the group consisting of greater than about 5%, greater than about 10%, greater than about 15%, greater than about 20%, greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 90%, greater than about 100%, greater than about 110%, greater than about 120%, greater than about 130%, greater than about 140%, and greater than about 150%, than the mean C_{max} exhibited by a standard commercial, non-nanoparticulate composition of megestrol, administered at the same dosage.

20. The method of claim **1**, wherein there is a difference in absorption (AUC) when the composition is administered in fed versus fasted states, and the difference is selected from the group consisting of less than about 35%, less than about 30%, less than about 25%, less than about 20%, less than about 15%, less than about 10%, less than about 5%, and less than about 3%.

21. The method of claim **4**, wherein the anorexia, cachexia or loss of body mass is associated with a diagnosis of HIV or AIDS in the human patient.

22. The method of claim **4**, wherein the anorexia, cachexia or loss of body mass is associated with a diagnosis of cancer in the human patient.

23. The method of claim **4**, wherein the anorexia, cachexia or loss of body mass is associated with cancer.

24. The method of claim **4**, wherein the anorexia, cachexia or loss of body mass is associated with HIV or AIDS.

25. The method of claim **4**, wherein a maximum blood plasma concentration of megestrol is attained in about 1 hour or less after administration of the megestrol formulation in fasting subjects.

26. The method of claim **4**, wherein a maximum blood plasma concentration of megestrol of at least about 700 ng/ml is obtained.

27. The method of claim **26**, wherein the maximum blood plasma concentration of megestrol is at least about 700 ng/ml and is attained in less than 5 hours after administration of the megestrol formulation.

28. The method of claim **4**, wherein the maximum blood plasma concentration of megestrol is at least about 400 ng/ml and is attained in less than 5 hours after administration of the megestrol formulation.

29. The method of claim **4**, wherein a mean C_{max} of about 300 ng/ml to about 2000 ng/ml is obtained after a single administration of the formulation in the human subject in a fasted state.

30. The method of claim **4**, wherein the surface stabilizer is selected from the group consisting of nonionic, cationic, ionic, and zwitterionic surfactants.

31. The method of claim **4**, wherein the surface stabilizer is selected from the group consisting of hydroxypropyl methylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, sodium lauryl sulfate, dioctylsulfosuccinate, gelatin, casein, lecithin, dextran, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose phthalate, noncrystalline cellulose, magnesium aluminium silicate, triethanolamine, polyvinyl alcohol (PVA), 4-(1,1,3,3-tetramethylbutyl)-phenol polymer with ethylene oxide and formaldehyde, poloxamers, poloxamines, Tetronic 1508, alkyl aryl polyether sulfonate, mixture of sucrose stearate and sucrose distearate, p-isononylphenoxypoly-(glycidol), $C_{18}H_{37}CH_2(CON(CH_3)—CH_2(CHOH)_4(CH_2OH)_2$, decanoyl-N-methylglucamide; n-decyl β-D-glucopyranoside; n-decyl β-D-maltopyranoside; n-dodecyl β-D-glucopyranoside; n-dodecyl β-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-β-

D-glucopyranoside; n-heptyl β-D-thioglucoside; n-hexyl β-D-glucopyranoside; nonanoyl-N-methylglucamide; n-noyl β-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl-β-D-glucopyranoside; octyl β-D-thioglucopyranoside; PEG-phospholipid, PEG-cholesterol, PEG-cholesterol derivative, PEG-vitamin A, PEG-vitamin E, lysozyme, random copolymers of vinyl pyrrolidone and vinyl acetate, biopolymers, polysaccharides, cellulosics, alginates, phospholipids, poly-n-methylpyridinium, anthryul pyridinium chloride, chitosan, polylysine, polyvinylimidazole, polybrene, polymethylmethacrylate trimethylammoniumbromide bromide, hexyldesyltrimethylammonium bromide, polyvinylpyrrolidone-2-dimethylaminoethyl methacrylate dimethyl sulfate, stearyltrimethylammonium chloride, benzyl-di(2-chloroethyl)ethylammonium bromide, coconut trimethyl ammonium chloride or bromide, coconut methyl dihydroxyethyl ammonium chloride or bromide, decyl triethyl ammonium chloride, decyl dimethyl hydroxyethyl ammonium chloride or bromide, C_{12-15} dimethyl hydroxyethyl ammonium chloride or bromide, coconut dimethyl hydroxyethyl ammonium chloride or bromide, myristyl trimethyl ammonium methyl sulphate, lauryl dimethyl benzyl ammonium chloride or bromide, lauryl dimethyl (ethenoxy)$_4$ ammonium chloride or bromide, N-alkyl (C_{12-18}) dimethylbenzyl ammonium chloride, N-alkyl (C_{14-18})dimethyl-benzyl ammonium chloride, N-tetradecylidmethylbenzyl ammonium chloride monohydrate, dimethyl didecyl ammonium chloride, N-alkyl and (C_{12-14}) dimethyl 1-napthylmethyl ammonium chloride, trimethylammonium halide, alkyl-trimethylammonium salts and dialkyl-dimethylammonium salts, lauryl trimethyl ammonium chloride, ethoxylated alkyamidoalkyldialkylammonium salt and/or an ethoxylated trialkyl ammonium salt, dialkylbenzene dialkylammonium chloride, N-didecyldimethyl ammonium chloride, N-tetradecyldimethylbenzyl ammonium, chloride monohydrate, N-alkyl(C_{12-14}) dimethyl 1-naphthylmethyl ammonium chloride and dodecyldimethylbenzyl ammonium chloride, dialkyl benzenealkyl ammonium chloride, lauryl trimethyl ammonium chloride, alkylbenzyl methyl ammonium chloride, alkyl benzyl dimethyl ammonium bromide, C_{12}, C_{15}, C_{17} trimethyl ammonium bromides, dodecylbenzyl triethyl ammonium chloride, poly-diallyldimethylammonium chloride (DADMAC), dimethyl ammonium chlorides, alkyldimethylammonium halogenides, tricetyl methyl ammonium chloride, decyltrimethylammonium bromide, dodecyltriethylammonium bromide, tetradecyltrimethylammonium bromide, methyl trioctylammonium chloride, tetrabutylammonium bromide, benzyl trimethylammonium bromide, choline esters, benzalkonium chloride, stearalkonium chloride compounds, cetyl pyridinium bromide, cetyl pyridinium chloride, halide salts of quaternized polyoxyethylalkylamines, alkyl pyridinium salts, alkylamines, dialkylamines, alkanolamines, polyethylenepolyamines, N,N-dialkylaminoalkyl acrylates, vinyl pyridine, lauryl amine acetate, stearyl amine acetate, alkylpyridinium salt, alkylimidazolium salt, imide azolinium salts; protonated quaternary acrylamides; methylated quaternary polymers, and cationic guar.

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